

**THIONE DERIVATIVES, PROCESSES FOR THE PREPARATION
THEREOF, AND PHARMACEUTICAL COMPOSITIONS CONTAINING
THE SAME**

5 Technical Field

The present invention relates to a thione derivative or a non-toxic salt thereof which is effective in reduce inflammation, pain, or fever, a method for preparing the same, and a pharmaceutical composition containing the same as an active ingredient.

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Background Art

Most nonsteroidal antiinflammatory agents are responsible for blocking enzyme, cyclooxygenase (COX) or prostaglandin G/H synthase, to reduce inflammation, pain, or fever. In addition, they inhibit uterus contraction caused by hormones and also inhibit growth of several cancers. Cyclooxygenase-1 (COX-1) was first discovered in bovine. The COX-1 is constitutively expressed in a variety of cell types. Unlike the COX-1, cyclooxygenase-2 (COX-2) is a recently discovered isoform of cyclooxygenase that can be easily induced by mitogen, endotoxin, hormone, growth factor, or cytokine.

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Prostaglandin is a potent mediator for various pathological and physiological processes. The COX-1 plays important physiological roles such as in the release of endogenous prostaglandin, the maintenance of the shape and the function of stomach, and the blood circulation in the kidney. On the other hand, the COX-2 is induced by an inflammatory factor, hormone, a growth factor, or cytokine. Therefore, the COX-2 is involved in pathological processes of prostaglandin, unlike the constitutive COX-1. In this regard, selective inhibitors of the COX-2 produce fewer and less side effects in terms of action mechanism in comparison with conventional nonsteroidal antiinflammatory agents. In addition, they reduce inflammation, pain, and fever and inhibit uterus contraction caused by hormones and growth of several cancers. In particular, they are effective in decreasing side effects such as stomach toxicity and kidney toxicity. Still furthermore, they inhibit the synthesis of contractile prostanoid, thereby leading to suppression of the contraction

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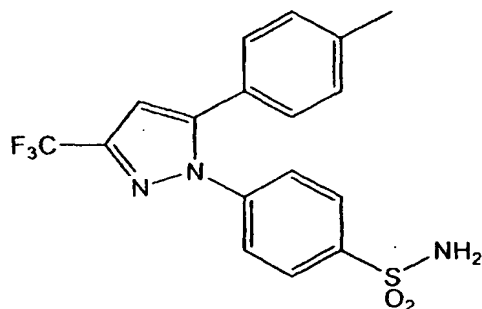
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In addition, it is anticipated that selective inhibitors of the COX-2 would be effective in treating osteoporosis and glaucoma. Utility of selective inhibitors of the COX-2 is well described in publications [John Vane, "Towards a Better Aspirin" in *Nature*, Vol.367, pp215-216, 1994; Bruno Battistini, Regina Botting and Y.S. Bakhle, "COX-1 and COX-2: Toward the Development of More Selective NSAIDs" in *Drug News and Perspectives*, Vol.7, pp501-512, 1994; Urology, Vol.58, pp127, 2001; David B. Reitz and Karen Seibert, "Selective Cyclooxygenase Inhibitors" in *Annual Reports in Medicinal Chemistry*, James A. Bristol, Editor, Vol. 30, pp179-188, 1995].

Various selective COX-2 inhibitors having different structures are known. Among them, a selective COX-2 inhibitor having a diaryl heterocyclic structure, i.e. a tricyclic structure has been widely studied as a potent candidate. The diaryl heterocyclic structure has a central ring and a sulfonamide or methylsulfone group attached to one of the aryl rings.

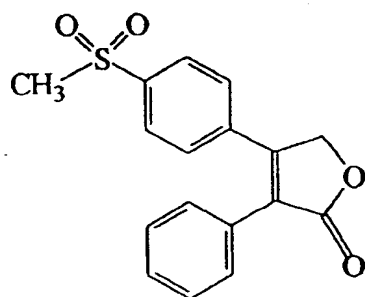
One selective COX-2 inhibitor, Celecoxib of formula 87 is disclosed in U.S. Patent No. 5,466,823. The Celecoxib is a substituted pyrazolyl benzenesulfonamide derivative.

Formula 87



Another selective COX-2 inhibitor, Rofecoxib of formula 88 is disclosed in WO 95/00501. The Rofecoxib has a diaryl heterocyclic structure with a central furanone ring.

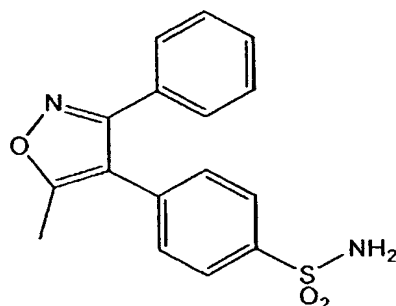
Formula 88



Valdecoxib of formula 89 as another selective COX-2 inhibitor is disclosed in U.S. Patent No. 5,633,272. The Valdecoxib has a phenylsulfonamide moiety with a central isoxazole ring.

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Formula 89



The selective COX-2 inhibitors of formulas 87 to 89 are effective inflammatory therapeutic agents with fewer and less side effects in comparison with conventional nonsteroidal antiinflammatory agents.

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Disclosure of the Invention

An aspect of the present invention provides a thione derivative of formula 1 or a non-toxic salt thereof.

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Another aspect of the present invention provides a method for preparing a thione derivative or a non-toxic salt thereof.

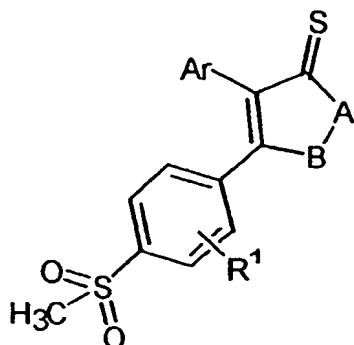
Another aspect of the present invention provides a pharmaceutical composition comprising a thione derivative or a non-toxic salt thereof as an active ingredient for the treatment of fever, pain, and inflammation.

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Best mode for carrying out the invention

According to an aspect of the present invention, there is provided a thione derivative represented by formula 1:

Formula 1



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wherein:

A and B each independently represent O, S, NR²; wherein R² represents hydrogen, C₁-C₄ alkyl, C₁-C₄ alkenyl, or aryl;

Ar represents aryl; heteroaryl; aryl or heteroaryl substituted with
 10 one to five radicals independently selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, trifluoromethyl, nitro, acetoxy, amino, C₁-C₃ alkylamino, C₁-C₃ dialkylamino, hydroxy, C₁-C₃ hydroxyalkyl, and thioxy; and

R¹ represents hydrogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, cyano,
 15 nitro, hydroxy, amino, C₁-C₄ alkylamino, or C₁-C₄ dialkylamino;
 or a non-toxic salt thereof.

Preferably, A and B each independently represent S or NH;

Ar represents phenyl; phenyl substituted with one to five radicals
 20 independently selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, trifluoromethyl, acetoxy, and nitro; pyridyl; or naphthyl;
 and

R¹ represents hydrogen or halogen.

The thione derivative of formula 1 may be present in a form of a
 non-toxic salt. The term, "non-toxic salt" as used herein refers to a
 25 pharmaceutically acceptable, toxin-free salt, including an organic salt
 and an inorganic salt.

The thione derivative of formula 1 may be present in a form of an
 organic acid salt or an inorganic acid salt.

Examples of the organic acid salt or the inorganic acid salt of the thione derivative of formula 1 include, but are not limited to, a salt of acetic acid, adipic acid, aspartic acid, 1,5-naphthalene disulfonic acid, benzene sulfonic acid, benzoic acid, camphor sulfonic acid, citric acid, 5 1,2-ethane disulfonic acid, ethane sulfonic acid, ethylenediaminetetraacetic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, hydroiodic acid, hydrobromic acid, hydrochloric acid, icethionic acid, lactic acid, maleic acid, malic acid, maledic acid, methane sulfonic acid, mucinic acid, 10 2-naphthalenedisulfonic acid, nitric acid, oxalic acid, pentothenic acid, phosphoric acid, pivalic acid, propionic acid, salicylic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid, p-toluene sulfonic acid, undecanoic acid, and 10-undecenoic acid. Preferably, a salt of succinic acid, hydrobromic acid, hydrochloric acid, maleic acid, methanesulfonic acid, phosphoric acid, sulfuric acid, or tartaric acid is used.

The thione derivative of the present invention preferably includes:

4-(4-ethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;

4-(4-bromophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;

5-(4-methanesulfonylphenyl)-4-toryl-[1,2]dithiol-3-thione;

5-(4-methanesulfonylphenyl)-4-phenyl-[1,2]dithiol-3-thione;

5-(4-methanesulfonylphenyl)-4-methoxyphenyl-[1,2]dithiol-3-thione;

5-(4-methanesulfonylphenyl)-4-(2-trifluoromethylphenyl)-[1,2]dithiol-3-thione;

4-(4-chlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;

4-(3,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;

5-(4-methanesulfonylphenyl)-4-pyridine-4-yl-[1,2]dithiol-3-thione;

5-(4-methanesulfonylphenyl)-4-pyridine-3-yl-[1,2]dithiol-3-thione;

5-(4-methanesulfonylphenyl)-4-pyridine-2-yl-[1,2]dithiol-3-thione;

4-(4-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;

4-(2,5-dimethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;

4-(3,5-dimethylphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;
 5-(4-methanesulfonylphenyl)-4-(3-methoxyphenyl)-[1,2]dithiol-3-thione;
 5-(4-methanesulfonylphenyl)-4-(2-nitrophenyl)-[1,2]dithiol-3-thione;
 5-(4-methanesulfonylphenyl)-4-(3-trifluoromethylphenyl)-[1,2]dithiol-3-thione;
 5-(4-methanesulfonylphenyl)-4-o-toryl-[1,2]dithiol-3-thione;
 4-(2-chlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;
 4-(2,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;
 4-(2-chloro-4-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;
 4-(3,4-dimethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;
 4-(2-bromophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;
 4-(2-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;
 4-(2,4-difluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;
 4-(3,4-difluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;
 5-(4-methanesulfonylphenyl)-4-naphthalene-2-yl-[1,2]dithiol-3-thione;
 5-(4-methanesulfonylphenyl)-4-pentafluorophenyl-[1,2]dithiol-3-thione;
 4-(4-isopropoxylphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;
 5-(4-methanesulfonylphenyl)-4-(4-propoxyphenyl)-[1,2]dithiol-3-thione;
 acetic acid 4-[5-(4-methanesulfonylphenyl)-3-thioxo-3H-[1,2]dithiol-4-yl]phenyl ester;
 5-(2-chloro-4-methanesulfonylphenyl)-4-(4-ethoxyphenyl)-[1,2]dithiol-3-thione;

5-(2-chloro-4-methanesulfonylphenyl)-4-*p*-toryl-[1,2]dithiol-3-thione;
e;

4-(4-bromophenyl)-5-(2-chloro-4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;

5 5-(2-chloro-4-methanesulfonylphenyl)-4-(4-methoxyphenyl)-[1,2]dithiol-3-thione;

5-(3-fluoro-4-methanesulfonylphenyl)-4-*p*-toryl-[1,2]dithiol-3-thione

10 5-(3-fluoro-4-methanesulfonylphenyl)-4-(4-methoxyphenyl)-[1,2]dithiol-3-thione;

acetic acid 4-[5-(3-fluoro-4-methanesulfonylphenyl)-3-thioxo-3H-[1,2]dithiol-4-yl]-phenyl ester;

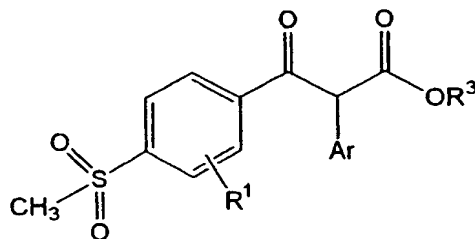
5-(4-methanesulfonylphenyl)-4-*p*-toryl-1,2-dihydropyrazole-3-thione;
e;

15 4-(3,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-1,2-dihydropyrazole-3-thione; and

4-(4-chlorophenyl)-5-(4-methanesulfonylphenyl)-1,2-dihydropyrazole-3-thione.

20 According to another aspect of the present invention, there is provided a propionic acid derivative as an intermediate for the synthesis of the thione derivative of formula 1, as represented by formula 2:

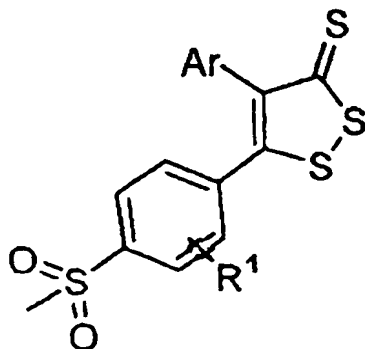
Formula 2



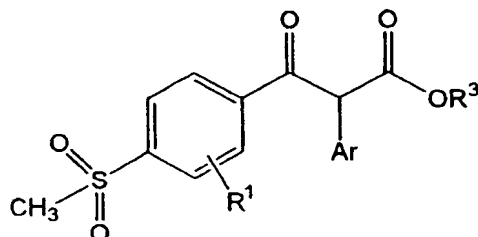
25 wherein, R^1 and Ar are as defined in formula 1 and R^3 represents C_1 - C_4 alkyl.

According to another aspect of the present invention, there is provided A method for preparing a thione derivative of formula 1a or a non-toxic salt thereof, comprising reacting a propionic acid derivative of formula 2 with phosphorus pentasulfide, Lawesson's Reagent,
30 beta-oxothiostic acid, or potassium beta-oxothiostate:

Formula 1a



Formula 2



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wherein:

 R^1 and Ar are as defined in claim 1; R^3 represents C_1 - C_3 alkyl.

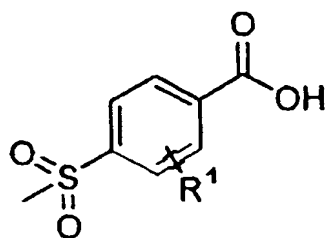
Among phosphorus pentasulfide, Lawesson's Reagent, beta-oxothioctic acid, or potassium beta-oxothioctate, which is used to introduce thione structure, phosphorus pentasulfide is most preferred.

The said reaction is commonly carried out in an unreactive organic solvent, which includes but is not limited to benzene, toluene, and xylene. Among them, toluene is most preferred.

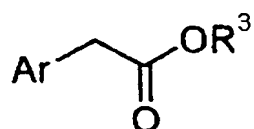
The said reactions may be completed by heating the solvent to its boiling point. For example, when toluene is used as a solvent, the reaction may be completed by heating toluene to the boiling point and refluxing it.

The above propionic acid derivative of formula 2 may be prepared by reacting a methanesulfonylbenzoic acid derivative of formula 3 with an aryl acetate derivative of formula 4 in the presence of a base;

Formula 3



Formula 4

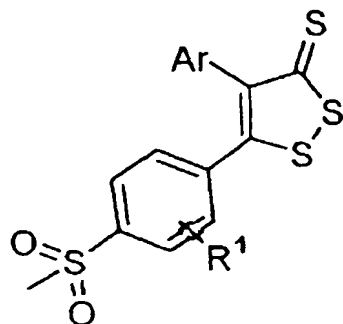


5 wherein, R¹ and Ar are as defined in formula 1 and R³ represents C₁-C₄ alkyl.

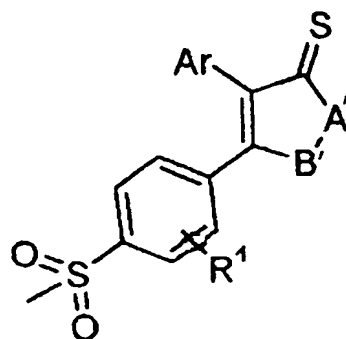
The said base includes, but is not limited to sodium hydride, potassium carbonate, or potassium hydroxide. Preferably, sodium hydride is used.

10 According to another aspect of the present invention, there is provided a method for preparing a thione derivative of formula 1b or a non-toxic salt thereof, comprising reacting a thione derivative of formula 1a with NHR²NHR² or NHR²OH in the presence of a base:

15 Formula 1a



Formula 1b



wherein, A' and B' each independently represent S or NR²,
 provided that A' and B' are not simultaneously S; and Ar and R² are as
 5 defined in formula 1.

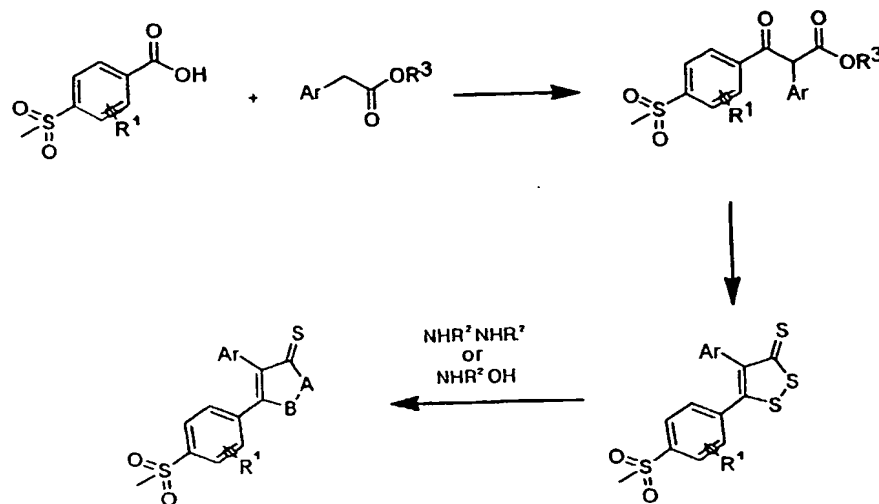
The said base includes, but is not limited to calcium carbonate,
 potassium hydroxide, or sodium hydroxide. Preferably, potassium
 hydroxide is used.

The separation and purification of the reaction products can be
 10 performed by concentration, extraction, or other processes, which is
 conventionally used in organic synthesis process, and optionally by a
 silica gel column chromatography.

A preferred embodiment of the method for preparing a compound
 of formula 1a and formula 1b is expressed by the following scheme 1:

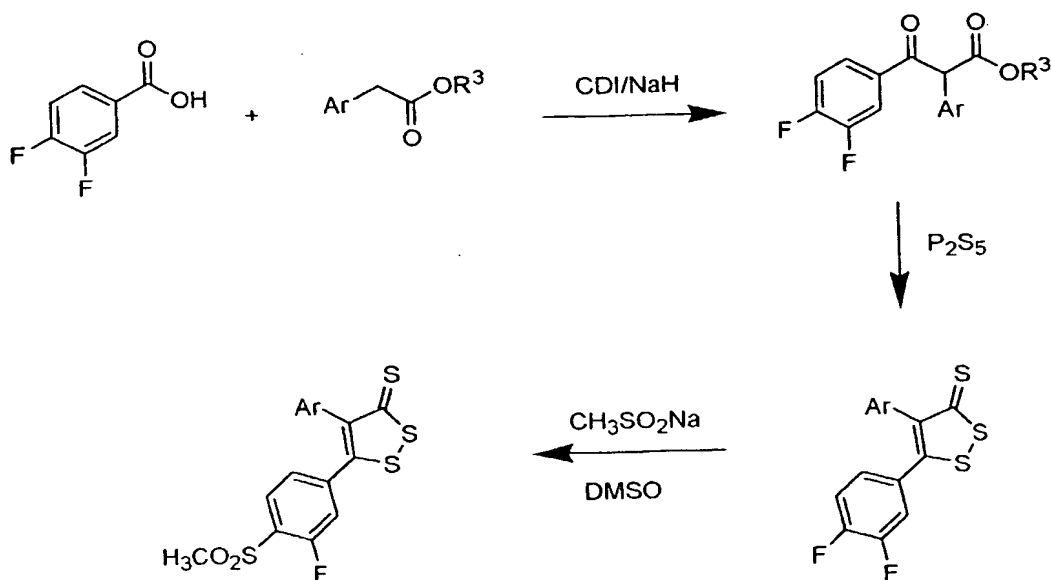
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Reaction formula 1



wherein, A, B, Ar, R^1 , R^2 , and R^3 are as defined in the above.

When R^1 is fluorine in the formula 1a of the present invention, the method for preparing a compound of the present invention may be expressed by the following scheme 2:



wherein, Ar and R^3 are as defined in the above.

According to another aspect of the present invention, there is provided a pharmaceutical composition comprising a therapeutically

effective amount of a thione derivative of formula 1 or a non-toxic salt thereof as an active ingredient and a pharmaceutically acceptable carrier for treatment of fever, pain, and inflammation.

5 The pharmaceutical composition comprises a compound of formula 1 or a non-toxic salt thereof when it is a selective inhibitor of cyclooxygenase-2. Therefore, the pharmaceutical composition can be used as an antipyretic, an analgesic, and an antiinflammatory agent, with reduced side effects.

10 Conventional nonsteroidal antiinflammatory agents non-selectively inhibit the prostaglandin synthesis enzymes, cyclooxygenase-1 and cyclooxygenase-2. Therefore, various side effects may occur.

On the other hand, a compound of formula 1 and a non-toxic salt thereof selectively inhibit cyclooxygenase-2. Therefore, the side effects of conventional nonsteroidal antipyretics, analgesics, and
15 antiinflammatory agents can be reduced.

The pharmaceutical composition of the present invention comprises a compound of formula 1 and/or a non-toxic salt thereof and a pharmaceutically acceptable carrier or excipient. Therefore, the pharmaceutical composition may be used as a substitute for
20 conventional nonsteroidal antiinflammatory agents. In particular, due to the reduction of the side effects of conventional nonsteroidal antipyretics, analgesics, and antiinflammatory agents, the pharmaceutical composition of the present invention is useful in treating patients with peptic ulcer, gastritis, regional enteritis, ulcerative colitis, diverticulitis,
25 gastrorrhagia, or hypoprothrombinemia.

The pharmaceutical composition of the present invention can be used in all inflammatory diseases associated with pathological prostaglandin and is particularly useful in treating osteoarthritis and rheumatoid arthritis which require high dosage of nonsteroidal
30 antiinflammatory agents.

The pharmaceutical composition of the present invention can be administered in the form of an adult dosage of 1 mg/day to 1000 mg/day of the compound of formula 1. An adequate dosage is determined depending on the degree of disease severity.

35 The pharmaceutical composition of the present invention may be administered in the form of tablet, foam tablet, capsule, granule, powder, sustained-release tablet, sustained-release capsule (a single unit

formulation or a multiple unit formulation), intravenous and intramuscular injectable solution, infusion solution, suspension, or suppository, or in other suitable dosage forms.

5 Sustained-release pharmaceutical dosage forms contain active ingredients with or without an initial loading dose. They are wholly or partially sustained-release pharmaceutical dosage forms to release active ingredients in a controlled manner.

Preferably, the pharmaceutical composition is orally administered.

10 The pharmaceutical composition further comprises a pharmaceutically acceptable excipient and/or diluent and/or adjuvant in pharmaceutically effective amounts.

Examples of the excipient and adjuvant include gellatin, a natural sugar such as sucrose and lactose, lecitin, pectin, starch such as corn starch and amylose, cyclodextrin and cyclodextrin derivative, dextran, 15 polyvinylpyrrolidone, polyvinyl acetate, Arabic gum, arginic acid, xylose, talc, salicylic acid, calcium hydrogen phosphate, cellulose, cellulose derivative such as methylcellulose, methoxypropyl cellulose, hydroxypropylmethyl cellulose, and hydroxypropylmethylcellulose phthalate, fatty acid having 12 to 22 carbon atoms, emulsifying agent, oil 20 and fat, in particular, vegetable glycerol ester and polyglycerol ester of saturated fatty acids, monohydric alcohol, polyhydric alcohol, polyglycol such as polyethylene glycol, aliphatic alcohol having 1 to 20 carbon atoms, or aliphatic saturated or unsaturated fatty acid ester having 2 to 22 carbon atoms with polyhydric alcohols such as glycol, glycerol, 25 diethylene glycol, 1,2-propylene glycol, sorbitol, and mannitol.

Other suitable adjuvants include a disintegrating agent. Examples of the disintegrating agent include a cross-linked polyvinylpyrrolidone, sodium carboxymethyl starch, sodium carboxymethyl cellulose, and microcrystalline cellulose. A coating agent 30 which is conventionally used in this field may also be used. Examples of the coating agent include acrylic acid and/or methacrylic acid and/or an ester polymer or copolymer thereof, zein, ethyl cellulose, ethyl cellulose succinate, and Shellac.

A plasticizer suitable for the coating agent is citric ester and 35 tartaric ester, glycerol and glycerol ester, or polyethylene glycol with different chain lengths.

A liquid composition such as solution and suspension is formulated in water or a physiological acceptable organic solvent such as alcohol and aliphatic alcohol.

The liquid pharmaceutical composition may further comprise a preservative such as potassium solvate, methyl 4-hydroxybenzoate, and propyl 4-hydroxybenzoate, an antioxidant such as ascorbic acid, and a fragrant such as peppermint oil.

In addition, when the liquid pharmaceutical composition is formulated, a conventional solubilizer or emulsifier such as polyvinylpyrrolidone and polysolvate 80 may be used.

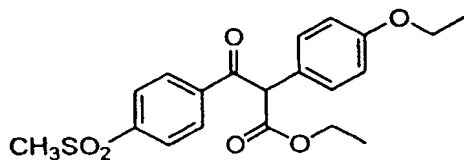
Other examples of suitable excipients and adjuvants are disclosed in Dr.H.P. Fielder, "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete" [Encyclopaedia of auxiliaries for pharmacy, cosmetics and related fields].

Hereinafter, the present invention will be described more specifically by examples. However, the following examples are provided only for illustration and thus the present invention is not limited to or by them.

Example 1

2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 5



499 mg of 4-ethoxyphenylacetic acid ethyl ester, 480 mg of carbonyldiimidazole, and 0.5 g of 4-methanesulfonyl benzoic acid were dissolved in 10 ml of dimethyl formamide, and 119 mg of sodium hydride were slowly added dropwise to the solution and the mixture was reacted at the room temperature for 12 hours. Afterwards, water was added to dilute the resultant, followed by extraction with ethyl acetate. The obtained organic layer was dried over anhydrous magnesium sulfate to give 0.9 g of the titled compound as a light yellow liquid (yield 92%).

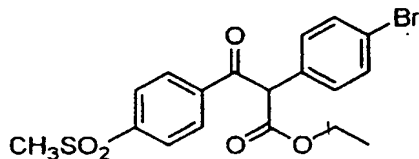
$^1\text{H-NMR}(400\text{MHz}, \text{CDCl}_3) \delta$ $^1\text{H-NMR}(400\text{MHz}, \text{CDCl}_3) \delta$ 8.14(d, 2H, $J=8.4\text{Hz}$), 8.04(d, 2H, $J=8.4\text{Hz}$), 6.95(d, 2H, $J=8.4\text{Hz}$), 6.65(d, 2H, $J=8.4\text{Hz}$), 5.56(s, 1H), 4.12(q, 2H, $J=6\text{Hz}$), 3.98(q, 2H, $J=6.0\text{Hz}$), 3.02(s, 3H), 1.33-1.31(m, 6H)

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Example 2

2-(4-bromophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 6



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1.2 g (yield 89%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 700 mg of 4-bromophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

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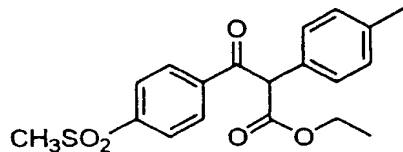
$^1\text{H-NMR}(400\text{MHz}, \text{CDCl}_3) \delta$ 8.15(d, 2H, $J=8.4\text{Hz}$), 8.05(d, 2H, $J=8.4\text{Hz}$), 6.97(d, 2H, $J=8.4\text{Hz}$), 6.94(d, 2H, $J=8.4\text{Hz}$), 5.55(s, 1H), 4.12(q, 2H, $J=6\text{Hz}$), 3.02(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 3

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3-(4-methanesulfonyl)-3-oxo-2-p-toryl-propionic acid ethyl ester

Formula 7



1.5 g (yield 83%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 890 mg of p-torylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

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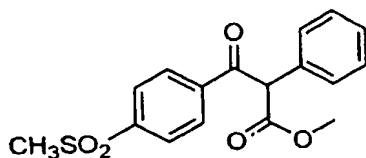
$^1\text{H-NMR}(400\text{MHz}, \text{CDCl}_3) \delta$ 8.14(d, 2H, $J=8.4\text{Hz}$), 8.03(d, 2H,

$J=8.4\text{Hz}$), 6.96(d, 2H, $J=8.4\text{Hz}$), 6.93(d, 2H, $J=8.4\text{Hz}$), 5.56(s, 1H), 4.12(q, 2H, $J=6\text{Hz}$), 3.02(s, 3H), 2.33(s, 2H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 4

5 3-(4-methanesulfonylphenyl)-3-oxo-2-phenylpropionic acid methyl ester

Formula 8



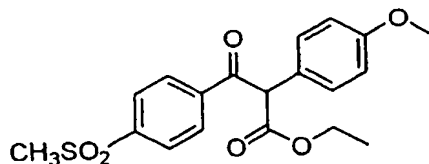
10 1.3 g (yield 80%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 940 mg of phenylacetic acid methyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.15(d, 2H, $J=8.4\text{Hz}$), 8.05(d, 2H, $J=8.4\text{Hz}$), 6.97-6.94(m, 5H), 5.56(s, 1H), 3.75(s, 3H), 3.02(s, 3H)

Example 5

15 3-(4-methanesulfonylphenyl)-2-(4-methoxyphenyl)-3-oxo-propionic acid ethyl ester

Formula 9



20 1.5 g (yield 83%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 970 mg of 4-methoxyphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

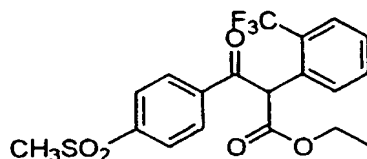
25 $^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.15(d, 2H, $J=8.4\text{Hz}$), 8.05(d, 2H, $J=8.4\text{Hz}$), 6.96(d, 2H, $J=8.4\text{Hz}$), 6.93(d, 2H, $J=8.4\text{Hz}$), 5.56(s, 1H),

4.12(q, 2H, $J=6.0\text{Hz}$), 3.79(s, 3H), 3.02(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 6

3-(4-methanesulfonylphenyl)-3-oxo-2-(2-trifluoromethylphenyl)-propionic acid ethyl ester

Formula 10



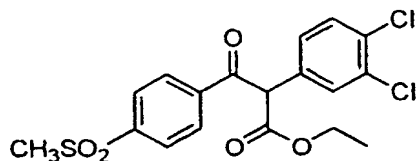
0.5 g (yield 65%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 900 mg of 2-trifluoromethylphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.14(d, 2H, $J=8.4\text{Hz}$), 8.04(d, 2H, $J=8.4\text{Hz}$), 7.33(d, 1H, $J=6.8\text{Hz}$), 7.14(t, 1H, $J=6.0\text{Hz}$), 7.00-7.68(m, 2H), 5.53(s, 1H), 4.12(q, 2H, $J=6.0\text{Hz}$), 3.02(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 7

2-(4-chlorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 11



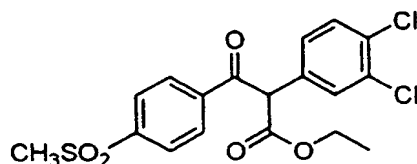
1.5 g (yield 78%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 990 mg of 4-chlorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.13(d, 2H, $J=8.4\text{Hz}$), 8.04(d, 2H, $J=8.4\text{Hz}$), 6.96(d, 2H, $J=8.4\text{Hz}$), 6.92(d, 2H, $J=8.4\text{Hz}$), 5.55(s, 1H), 4.12(q, 2H, $J=6.0\text{Hz}$), 3.02(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 8

2-(3,4-dichlorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

5 Formula 12



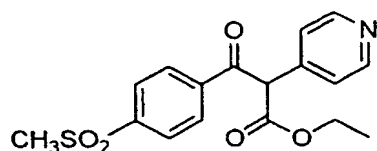
1.7 g (yield 85%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 990 mg of 3,4-dichlorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

¹H-NMR(400MHz, CDCl₃) δ 8.14(d, 2H, J=8.4Hz), 8.04(d, 2H, J=8.4Hz), 7.09(d, 1H, J=6.8Hz), 7.01(s, 1H), 6.88(d, 1H, J=6.8Hz), 5.53(s, 1H), 4.12(q, 2H, J=6.0Hz), 3.02(s, 3H), 1.33(t, 3H, J=4.0Hz)

15 Example 9

3-(4-methanesulfonylphenyl)-3-oxo-2-(pyridine-4-yl)-propionic acid ethyl ester

Formula 13



20 1.5 g (yield 78%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 800 mg of pyridine-4-yl-acetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

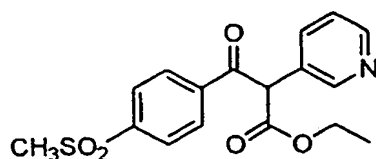
¹H-NMR(400MHz, CDCl₃) δ 8.55(d, 2H, J=4.00Hz), 7.85(d, 2H, J=9.2Hz), 7.39(d, 2H, J=9.2Hz), 6.99(d, 2H, J=4.0Hz), 5.50(s, 1H), 4.12(q, 2H, J=6.0Hz), 3.02(s, 3H), 1.33(t, 3H, J=4.0Hz)

Example 10

3-(4-methanesulfonylphenyl)-3-oxo-2-(pyridine-3-yl)-propionic acid
ethyl ester

5

Formula 14



1.35 g (yield 78%) of the titled compound as a liquid was prepared
in the same manner as in Example 1 except using 1 g of
pyridien-3-yl-acetic acid ethyl ester instead of 4-ethoxyphenylacetic acid
ethyl ester.

10

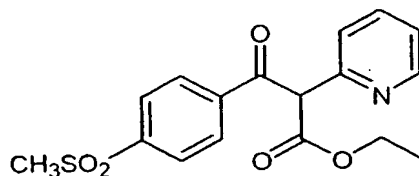
$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.56(s, 1H), 8.24(d, 1H, $J=4.0\text{Hz}$),
7.92(d, 2H, $J=8.0\text{Hz}$), 7.54(d, 1H, $J=4.0\text{Hz}$), 7.45(d, 2H, $J=8.0\text{Hz}$), 7.32(t,
1H, $J=6.0\text{Hz}$), 5.50(s, 1H), 4.12(q, 2H, $J=6.0\text{Hz}$), 3.03(s, 3H), 1.33(t, 3H,
 $J=4.0\text{Hz}$)

15

Example 11

3-(4-methanesulfonylphenyl)-3-oxo-2-(pyridine-2-yl)-propionic acid
ethyl ester

Formula 15



20

1.35 g (yield 78%) of the titled compound as a liquid was prepared
in the same manner as in Example 1 except using 1 g of
pyridine-2-yl-acetic acid ethyl ester instead of 4-ethoxyphenylacetic acid
ethyl ester.

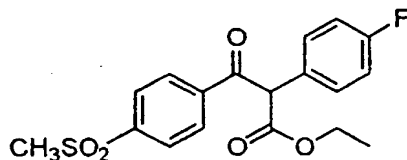
25

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.56(d, 1H, $J=6.8\text{Hz}$), 8.14(d, 2H,
 $J=8.4\text{Hz}$), 8.04(d, 2H, $J=8.4\text{Hz}$), 7.27-7.22(m, 3H), 5.56(s, 1H), 4.12(q,
2H, $J=6.0\text{Hz}$), 3.14(s, 3H), 1.37(t, 3H, $J=4.0\text{Hz}$)

Example 12

2-(4-fluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

5 Formula 16



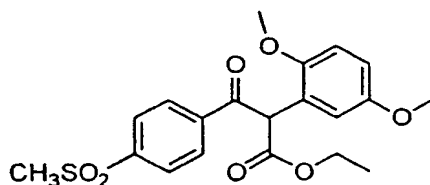
1.54 g (yield 85%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 1 g of 4-fluorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

¹H-NMR(400MHz, CDCl₃) δ 8.13(d, 2H, J=8.4Hz), 8.04(d, 2H, J=8.4Hz), 7.09-7.04(m, 4H), 5.55(s, 1H), 4.12(q, 2H, J=6.0Hz), 3.02(s, 3H), 1.33(t, 3H, J=4.0Hz)

15 Example 13

2-(2,5-dimethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 17



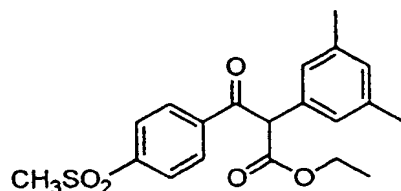
0.9 g (yield 90%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 560 mg of 2,5-dimethoxyphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

¹H-NMR(400MHz, CDCl₃) δ 8.13(d, 2H, J=8.4Hz), 8.04(d, 2H, J=8.4Hz), 6.96(d, 2H, J=8.4Hz), 6.92(d, 2H, J=8.4Hz), 5.55(s, 1H), 4.12(q, 2H, J=6.0Hz), 3.02(s, 3H), 1.33(t, 3H, J=4.0Hz)

Example 14

2-(3,5-dimethylphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 18



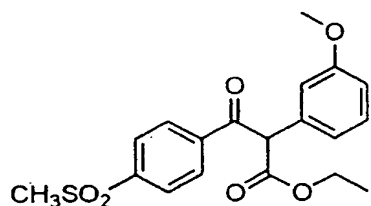
810 mg (yield 88%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 460 mg of 3,5-dimethylphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

¹H-NMR(400MHz, CDCl₃) δ 8.13(d, 2H, J=8.4Hz), 8.04(d, 2H, J=8.4Hz), 6.96(d, 2H, J=8.4Hz), 6.92(d, 2H, J=8.4Hz), 5.55(s, 1H), 4.12(q, 2H, J=6.0Hz), 3.02(s, 3H), 2.32(s, 6H), 1.33(t, 3H, J=4.0Hz)

Example 15

3-(4-methanesulfonylphenyl)-2-(3-methoxyphenyl)-3-oxo-propionic acid ethyl ester

Formula 19



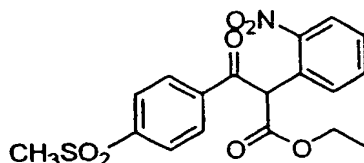
860 mg (yield 92%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 460 mg of 3-methoxyphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

¹H-NMR(400MHz, CDCl₃) δ 8.13(d, 2H, J=8.4Hz), 8.04(d, 2H, J=8.4Hz), 7.03(t, 1H, J=4.2Hz), 6.57-6.58(m, 3H), 5.55(s, 1H), 4.12(q,

2H, $J=6.0\text{Hz}$), 3.72(s, 3H), 3.02(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 16

3-(4-methanesulfonylphenyl)-2-(2-nitrophenyl)-3-oxo-propionic
 5 acid ethyl ester
 Formula 20

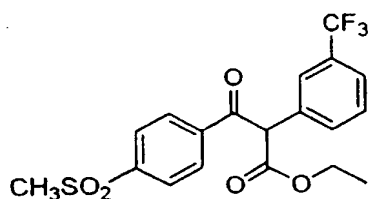


830 mg (yield 85%) of the titled compound as a liquid was
 prepared in the same manner as in Example 1 except using 500 mg of
 10 2-nitrophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid
 ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.13(d, 2H, $J=8.4\text{Hz}$), 8.07(d, 1H,
 $J=6.4\text{Hz}$), 8.04(t, 1H, $J=4.2\text{Hz}$), 7.53-7.52(m, 1H), 7.33-7.32(m, 2H),
 5.55(s, 1H), 4.12(q, 2H, $J=6.0\text{Hz}$), 3.02(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 17

3-(4-methanesulfonylphenyl)-3-oxo-2-(3-trifluoromethylphenyl)-pro
 pionic acid ethyl ester
 Formula 21



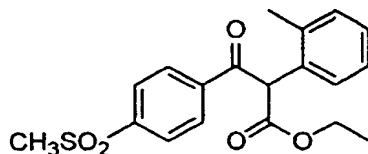
830 mg (yield 85%) of the titled compound as a liquid was
 prepared in the same manner as in Example 1 except using 500 mg of
 3-trifluoromethylphenylacetic acid ethyl ester instead of
 4-ethoxyphenylacetic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.13(d, 2H, $J=8.4\text{Hz}$), 8.04(d, 2H,
 $J=8.4\text{Hz}$), 7.26-7.25(m, 2H), 7.07-7.06(m, 2H), 5.55(s, 1H), 4.12(q, 2H,
 $J=6.0\text{Hz}$), 3.72(s, 3H), 3.02(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 18

3-(4-methanesulfonylphenyl)-3-oxo-2-o-toryl-propionic acid ethyl ester

5 Formula 22



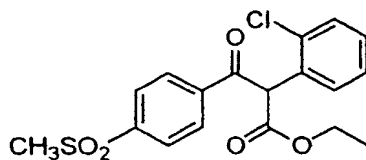
820 mg (yield 91%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 420 mg of o-torylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

¹H-NMR(400MHz, CDCl₃) δ 8.13(d, 2H, J=8.4Hz), 8.04(d, 2H, J=8.4Hz), 6.95-6.93(m, 4H), 5.55(s, 1H), 4.12(q, 2H, J=6.0Hz), 3.02(s, 3H), 2.35(s, 3H), 1.33(t, 3H, J=4.0Hz)

15 Example 19

2-(2-chlorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 23



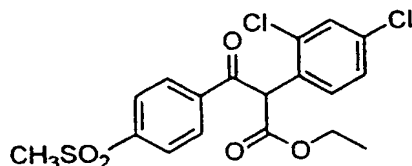
20 880 mg (yield 93%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 490 mg of 2-chlorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

¹H-NMR(400MHz, CDCl₃) δ 8.13(d, 2H, J=8.4Hz), 8.04(d, 2H, J=8.4Hz), 6.97-6.98(m, 4H), 5.55(s, 1H), 4.12(q, 2H, J=6.0Hz), 3.02(s, 3H), 1.33(t, 3H, J=4.0Hz)

Example 20

2-(2,4-dichlorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 24



5

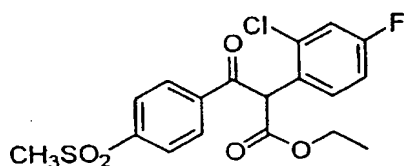
800 mg (yield 85%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 470 mg of 2,4-dichlorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

10 $^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.13(d, 2H, $J=8.4\text{Hz}$), 8.04(d, 2H, $J=8.4\text{Hz}$), 7.16(s, 1H), 7.03-7.01(m, 2H), 5.55(s, 1H), 4.12(q, 2H, $J=6.0\text{Hz}$), 3.02(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 21

15 2-(2-chloro-4-fluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 25



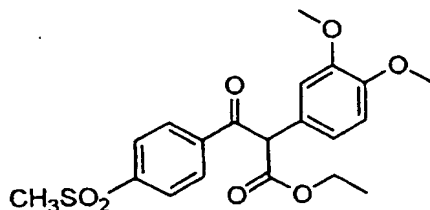
20 836 mg (yield 88%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 520 mg of 2-chloro-4-fluorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

25 $^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.13(d, 2H, $J=8.4\text{Hz}$), 8.04(d, 2H, $J=8.4\text{Hz}$), 6.98(t, 1H, $J=6.0\text{Hz}$), 6.86(d, 1H, $J=5.6\text{Hz}$), 6.73(d, 1H, $J=5.6\text{Hz}$), 5.55(s, 1H), 4.12(q, 2H, $J=6.0\text{Hz}$), 3.02(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 22

2-(3,4-dimethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 26



5

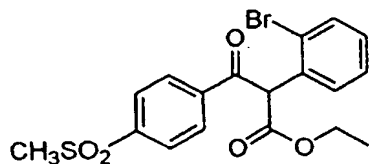
760 mg (yield 80%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 560 mg of 3,4-dimethoxyphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

10 $^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.13(d, 2H, $J=8.4\text{Hz}$), 8.04(d, 2H, $J=8.4\text{Hz}$), 6.53-6.51(m, 2H), 6.46(s, 1H), 5.55(s, 1H), 4.12(q, 2H, $J=6.0\text{Hz}$), 3.73(s, 6H), 3.02(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 23

15 2-(2-bromophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 27



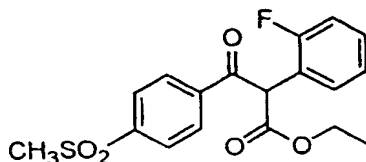
20 900 mg (yield 85%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 660 mg of 2-bromophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

25 $^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.13(d, 2H, $J=8.4\text{Hz}$), 8.04(d, 2H, $J=8.4\text{Hz}$), 6.99-6.97(m, 4H), 5.55(s, 1H), 4.12(q, 2H, $J=6.0\text{Hz}$), 3.02(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 24

2-(2-fluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic
acid ethyl ester

Formula 28



5

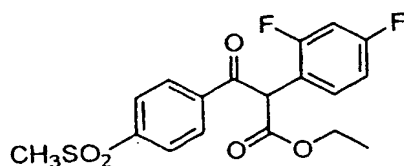
800 mg (yield 88%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 440 mg of 2-fluorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

10 $^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.13(d, 2H, $J=8.4\text{Hz}$), 8.04(d, 2H, $J=8.4\text{Hz}$), 7.03-7.01(m, 4H), 5.55(s, 1H), 4.12(q, 2H, $J=6.0\text{Hz}$), 3.02(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 25

15 2-(2,4-difluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 29



20 849 mg (yield 89%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 480 mg of 2,4-difluorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

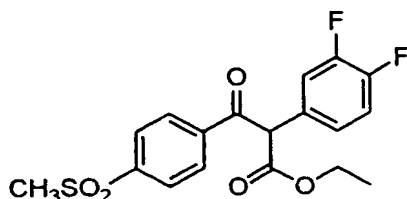
25 $^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.13(d, 2H, $J=8.4\text{Hz}$), 8.04(d, 2H, $J=8.4\text{Hz}$), 7.02-7.01(m, 2H), 6.56(m, 1H), 5.55(s, 1H), 4.12(q, 2H, $J=6.0\text{Hz}$), 3.02(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 26

2-(3,4-difluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

c acid ethyl ester

Formula 30



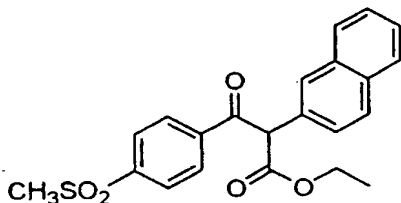
874 mg (yield 92%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 480 mg of 3,4-difluorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.13(d, 2H, $J=8.4\text{Hz}$), 8.04(d, 2H, $J=8.4\text{Hz}$), 6.83-6.81(m, 2H), 6.75(m, 1H), 5.55(s, 1H), 4.12(q, 2H, $J=6.0\text{Hz}$), 3.02(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 27

3-(4-methanesulfonylphenyl)-2-(naphthalene-2-yl)-3-oxo-propionic acid ethyl ester

Formula 31



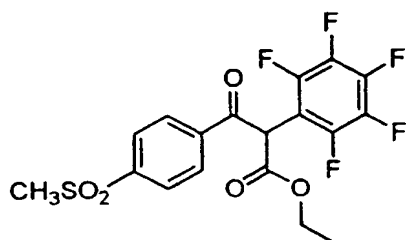
870 mg (yield 88%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 530 mg of naphthalene-2-yl-acetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.13(d, 2H, $J=8.4\text{Hz}$), 8.04(d, 2H, $J=8.4\text{Hz}$), 7.68-7.64(m, 3H), 7.46(s, 1H), 7.31-7.30(m, 2H), 7.16-7.15(m, 1H), 5.55(s, 1H), 4.12(q, 2H, $J=6.0\text{Hz}$), 3.02(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 28

3-(4-methanesulfonylphenyl)-3-oxo-2-pentafluorophenyl-propionic acid ethyl ester

Formula 32



5

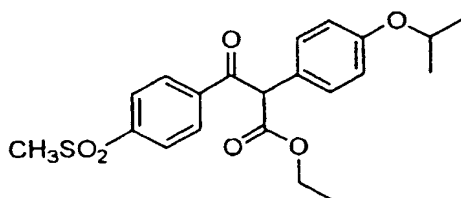
880 mg (yield 85%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 550 mg of pentafluorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

10 $^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.13(d, 2H, $J=8.4\text{Hz}$), 8.04(d, 2H, $J=8.4\text{Hz}$), 5.53(s, 1H), 4.12(q, 2H, $J=6.0\text{Hz}$), 3.01(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 29

15 2-(4-isopropoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 33



20 860 mg (yield 88%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 500 mg of 4-isopropoxyphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

25 $^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.14(d, 2H, $J=8.4\text{Hz}$), 8.04(d, 2H, $J=8.4\text{Hz}$), 6.95(d, 2H, $J=8.4\text{Hz}$), 6.65(d, 2H, $J=8.4\text{Hz}$), 5.56(s, 1H), 4.12(q, 2H, $J=6\text{Hz}$), 4.04-4.02(m, 1H), 3.02(s, 3H), 1.38(s, 3H), 1.37(s,

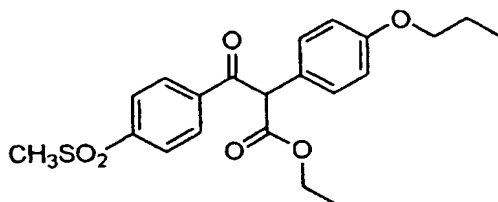
3H), 1.31(t, 3H, $J=4.0\text{Hz}$)

Example 30

3-(4-methanesulfonylphenyl)-3-oxo-2-(4-propoxyphenyl)-propionic

5 acid ethyl ester

Formula 34



890 mg (yield 92%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 500 mg of 4-propoxyphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

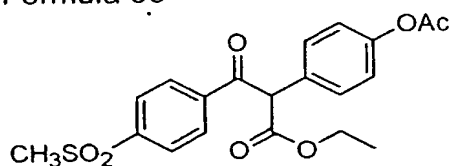
$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.14(d, 2H, $J=8.4\text{Hz}$), 8.04(d, 2H, $J=8.4\text{Hz}$), 6.95(d, 2H, $J=8.4\text{Hz}$), 6.65(d, 2H, $J=8.4\text{Hz}$), 5.56(s, 1H), 4.12(q, 2H, $J=6\text{Hz}$), 3.94-3.95(m, 2H), 3.02(s, 3H), 1.75-1.74(m, 2H), 1.30-1.28(m, 6H)

Example 31

2-(4-acetoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic

acid ethyl ester

20 Formula 35



848 mg (yield 84%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 500 mg of 4-acetoxyphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

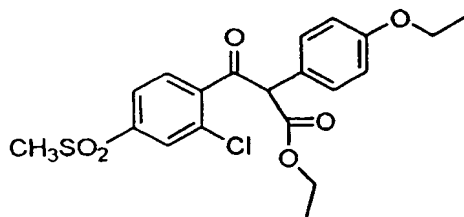
$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.14(d, 2H, $J=8.4\text{Hz}$), 8.04(d, 2H, $J=8.4\text{Hz}$), 7.03(d, 2H, $J=8.4\text{Hz}$), 6.95(d, 2H, $J=8.4\text{Hz}$), 5.56(s, 1h), 4.12(q,

2H, J=6.0Hz), 3.12(s, 3H), 2.08(s, 3H), 1.30(t, 3H, J=4.0Hz)

Example 32

3-(2-chloro-4-methanesulfonylphenyl)-2-(4-ethoxyphenyl)-3-oxo-propionic acid ethyl ester

Formula 36



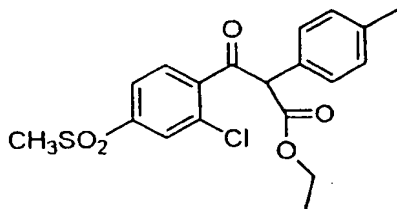
670 mg (yield 75%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 500 mg of 2-chloro-4-methanesulfonylbenzoic acid instead of 4-methanesulfonylbenzoic acid.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.08(d, 1H, $J=7.2\text{Hz}$), 8.05(s, 1H), 7.92(d, 1H, $J=7.2\text{Hz}$), 6.95-6.94(m, 4H), 5.56(s, 1H), 4.12(q, 2H, $J=6\text{Hz}$), 3.98(q, 2H, $J=6.0\text{Hz}$), 3.02(s, 3H), 1.33-1.31(m, 6H)

Example 33

3-(2-chloro-4-methanesulfonylphenyl)-3-oxo-2-p-toryl-propionic acid ethyl ester

Formula 37



740 mg (yield 88%) of the titled compound as a liquid was prepared in the same manner as in Example 3 except using 500 mg of 2-chloro-4-methanesulfonylbenzoic acid instead of 4-methanesulfonylbenzoic acid.

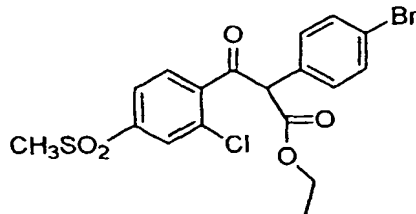
$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.08(d, 1H, $J=7.2\text{Hz}$), 8.05(s, 1H),

7.92(d, 1H, $J=7.2\text{Hz}$), 6.95-6.94(m, 4H), 5.56(s, 1H), 4.12(q, 2H, $J=6\text{Hz}$), 3.02(s, 3H), 2.35(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 34

5 2-(4-bromophenyl)-3-(2-chloro-4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 38



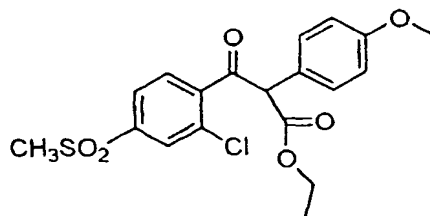
764 mg (yield 84%) of the titled compound as a liquid was prepared in the same manner as in Example 2 except using 500 mg of 2-chloro-4-methanesulfonylbenzoic acid instead of 4-methanesulfonylbenzoic acid.

$^1\text{H-NMR}(400\text{MHz}, \text{CDCl}_3)$ δ 8.08(d, 1H, $J=7.2\text{Hz}$), 8.05(s, 1H), 7.92(d, 1H, $J=7.2\text{Hz}$), 6.98-6.97(m, 4H), 5.55(s, 1H), 4.13(q, 2H, $J=6\text{Hz}$), 3.02(s, 3H), 1.33(t, 3H, $J=4.0\text{Hz}$)

Example 35

3-(2-chloro-4-methanesulfonylphenyl)-2-(4-methoxyphenyl)-3-oxo-propionic acid ethyl ester

20 Formula 39



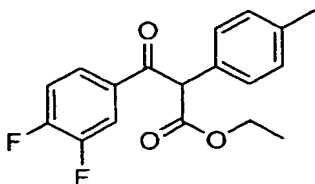
791 mg (yield 87%) of the titled compound as a liquid was prepared in the same manner as in Example 5 except using 500 mg of 2-chloro-4-methanesulfonylbenzoic acid instead of 4-methanesulfonylbenzoic acid.

$^1\text{H-NMR}(400\text{MHz}, \text{CDCl}_3)$ δ 8.08(d, 1H, $J=7.2\text{Hz}$), 8.05(s, 1H),

7.92(d, 1H, $J=7.2$ Hz), 6.95-6.94(m, 4H), 5.56(s, 1H), 4.13(q, 2H, $J=6$ Hz), 3.75(s, 3H), 3.02(s, 3H), 1.33(t, 3H, $J=4.0$ Hz)

Example 36

5 3-(3,4-difluorophenyl)-3-oxo-2-p-toryl-propionic acid ethyl ester
Formula 40



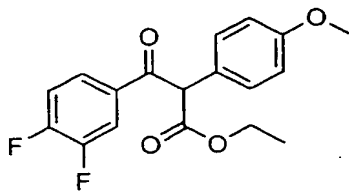
1.73 g (yield 82%) of the titled compound as a liquid was prepared in the same manner as in Example 3 except using 1 g of 3,4-difluorobenzoic acid instead of 4-methanesulfonylbenzoic acid.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.17(d, 2H, $J=7.6$ Hz), 7.05-7.03(m, 3H), 6.99(d, 2H, $J=7.6$ Hz), 5.52(s, 1H), 4.12(q, 2H, $J=6.0$ Hz), 2.35(s, 3H), 1.30(t, 3H, $J=4.0$ Hz)

15 Example 37

3-(3,4-difluorophenyl)-2-(4-methoxyphenyl)-3-oxo-propionic acid ethyl ester

Formula 41



20 850 mg (yield 85%) of the titled compound as a liquid was prepared in the same manner as in Example 5 except using 500 mg of 3,4-difluorobenzoic acid instead of 4-methanesulfonylbenzoic acid.

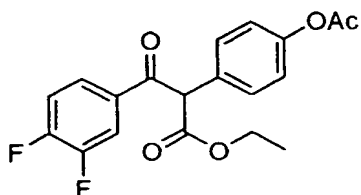
$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.16(d, 2H, $J=7.6$ Hz), 7.04-7.02(m, 3H), 6.99(d, 2H, $J=7.6$ Hz), 5.52(s, 1H), 4.12(q, 2H, $J=6.0$ Hz), 3.82(s, 3H), 1.30(t, 3H, $J=4.0$ Hz)

Example 38

2-(4-acetoxyphenyl)-3-(3,4-difluorophenyl)-3-oxo-propionic acid

ethyl ester

Formula 42



830 mg (yield 87%) of the titled compound as a liquid was prepared in the same manner as in Example 31 except using 416 mg of 3,4-difluorobenzoic acid instead of 4-methanesulfonylbenzoic acid.

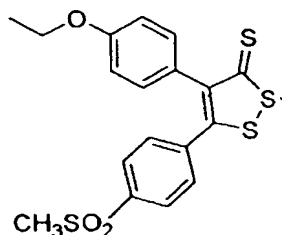
$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.17(d, 2H, $J=7.6\text{Hz}$), 7.05-7.03(m, 3H), 6.99(d, 2H, $J=7.6\text{Hz}$), 5.52(s, 1H), 4.12(q, 2H, $J=6.0\text{Hz}$), 2.32(s, 3H), 1.30(t, 3H, $J=4.0\text{Hz}$)

Example 39

4-(4-ethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thio

ne

Formula 43



0.68 g of phosphorus pentasulfide was dissolved in 10 ml of toluene, and then 0.3 g of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester was added thereto to reflux for 4 hours at 110°C . Afterwards the reaction apparatus was cooled, and ammonia water was added thereto slowly to adjust pH 8 to 8.5. The reaction mixture was diluted with water and extracted with ethyl acetate. The obtained organic layer was dried on anhydrous magnesium sulfate to distill the solvent. The resultant was recrystallized with n-hexane to give 180mg of the titled compound as a red solid(yield 60%).

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.88(d, 2H, $J=8.4\text{Hz}$), 7.45(d, 2H,

$J=8.4\text{Hz}$), 7.01(d, 2H, $J=6.8\text{Hz}$), 6.85(d, 2H, $J=6.8\text{Hz}$), 4.02(q, 2H, $J=6.8\text{Hz}$), 3.05(s, 3H), 1.42(t, 3H, $J=4.0\text{Hz}$)

El Mass(M^+) : 408

Melting point: 210-212 °C

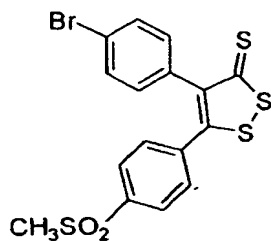
5

Example 40

4-(4-bromophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thio

ne

Formula 44



10

210 mg (yield 68%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(4-bromophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

15

$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.91(d, 2H, $J=8.4\text{Hz}$), 7.47(d, 2H, $J=8.4\text{Hz}$), 7.45(d, 2H, $J=8.4\text{Hz}$), 7.19(d, 2H, $J=8.4\text{Hz}$), 3.05(s, 3H)

El Mass(M^+) : 443

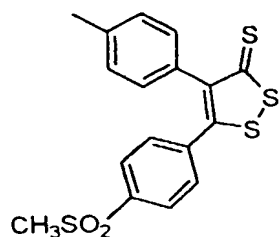
20

Melting point: 238-240 °C

Example 41

5-(4-methanesulfonylphenyl)-4-p-toryl-[1,2]dithiol-3-thione

Formula 45



25

200 mg (yield 65%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-p-toryl-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.89(d, 2H, $J=9.0\text{Hz}$), 7.46(d, 2H, $J=9.0\text{Hz}$), 7.16(d, 2H, $J=9.0\text{Hz}$), 6.99(d, 2H, $J=9.0\text{Hz}$), 3.05(s, 3H), 2.34(s, 3H)

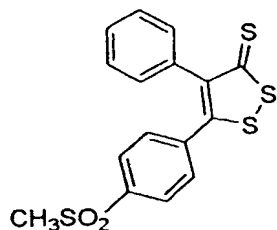
El Mass(M^+) : 378

Melting point: 240-242 $^\circ\text{C}$

Example 42

5-(4-methanesulfonylphenyl)-4-phenyl-[1,2]dithiol-3-thione

Formula 46



15

160 mg (yield 50%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-phenyl-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.87(d, 2H, $J=6.0\text{Hz}$), 7.44(d, 2H, $J=6.0\text{Hz}$), 7.35(t, 3H, $J=4.0\text{Hz}$), 7.12-7.10(m, 2H), 3.04(s, 3H)

El Mass(M^+) : 364

Melting point: 200-202 $^\circ\text{C}$

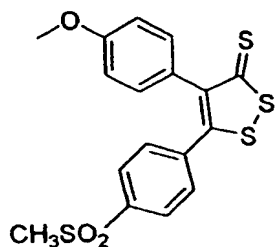
25

Example 43

5-(4-methanesulfonylphenyl)-4-(4-methoxyphenyl)-[1,2]dithiol-3-thi

one

Formula 47



120 mg (yield 40%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-2-(4-methoxyphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.90(d, 2H, $J=9.0\text{Hz}$), 7.46(d, 2H, $J=9.0\text{Hz}$), 7.04(d, 2H, $J=6.0\text{Hz}$), 6.88(d, 2H, $J=6.0\text{Hz}$), 3.81(s, 3H), 3.05(s, 3H)

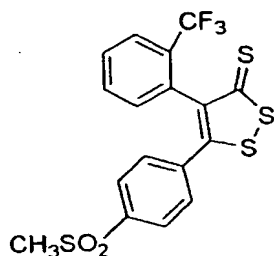
EI Mass(M^+) : 394

Melting point: 220-222 °C

Example 44

5-(4-methanesulfonylphenyl)-4-(2-trifluoromethylphenyl)-[1,2]dithiol-3-thione

Formula 48



160 mg (yield 51%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-(2-trifluoromethylphenyl)-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.92(d, 2H, $J=6.0\text{Hz}$), 7.63(d, 2H, $J=6.0\text{Hz}$), 7.46(d, 1H, $J=9.0\text{Hz}$), 7.35(d, 1H, $J=9.0\text{Hz}$), 7.24-7.21(m, 2H), 3.05(s, 3H)

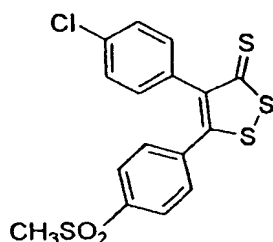
FAB Mass($M+1$) : 433

Melting point: 240-242 $^\circ\text{C}$

Example 45

4-(4-chlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione

Formula 49



180 mg (yield 45%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.4 g of 2-(4-chlorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.93(d, 2H, $J=8.0\text{Hz}$), 7.47(d, 2H, $J=8.0\text{Hz}$), 7.35(d, 2H, $J=8.0\text{Hz}$), 7.07(d, 2H, $J=8.0\text{Hz}$), 2.98(s, 3H)

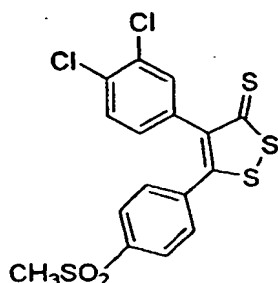
El Mass(M^+) : 399

Melting point: 233-235 $^\circ\text{C}$

Example 46

4-(3,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione

Formula 50



200 mg (yield 48%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.4 g of 2-(3,4-dichlorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

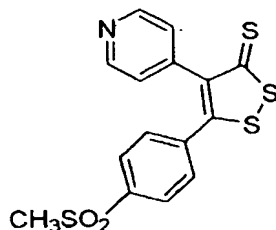
$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.98(d, 2H, $J=8.0\text{Hz}$), 7.49(d, 2H, $J=8.0\text{Hz}$), 7.44(d, 1H, $J=8.0\text{Hz}$), 7.35(s, 1H), 7.07(d, 1H, $J=8.0\text{Hz}$), 3.09(s, 3H)

El Mass(M^+) : 443

Example 47

5-(4-methanesulfonylphenyl)-4-(pyridine-4-yl)-[1,2]dithiol-3-thione

Formula 51



180 mg (yield 60%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-(pyridine-4-yl)-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 8.55(d, 2H, $J=4.0\text{Hz}$), 7.85(d, 2H,

$J=9.2\text{Hz}$), 7.39(d, 2H, $J=9.2\text{Hz}$), 6.99(d, 2H, $J=4.0\text{Hz}$), 2.98(s, 3H)

El Mass(M⁺) : 365

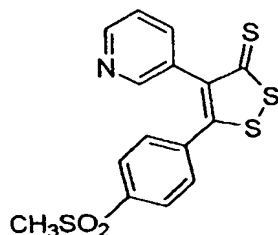
Melting point: 245-247 °C

5

Example 48

5-(4-methanesulfonylphenyl)-4-(pyridine-3-yl)-[1,2]dithiol-3-thione

Formula 52



10

189 mg (yield 61%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-(pyridine-3-yl)-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

15

¹H-NMR(300MHz, CDCl₃) δ 8.58(s, 1H), 8.25(d, 2H, $J=4.0\text{Hz}$), 7.92(d, 2H, $J=8.0\text{Hz}$), 7.54(d, 1H, $J=4.0\text{Hz}$), 7.45(d, 2H, $J=8.0\text{Hz}$), 3.03(s, 3H)

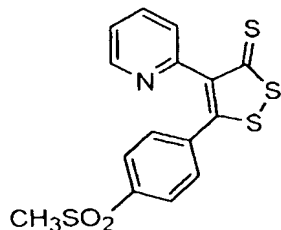
El Mass(M⁺) : 365

20

Example 49

5-(4-methanesulfonylphenyl)-4-(pyridine-2-yl)-[1,2]dithiol-3-thione

Formula 53



189 mg (yield 61%) of the titled compound as a liquid was

prepared in the same manner as in Example 39 except using 0.3 g of
 3-(4-methanesulfonylphenyl)-3-oxo-2-(pyridine-2-yl)-propionic acid ethyl
 ester instead of
 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid
 ethyl ester.

$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 8.55(m, 1H), 7.87(dt, 2H, $J=8.6\text{Hz}$,
 $J=2.1\text{Hz}$), 7.75(ddd, 1H, $J=9.5\text{Hz}$, $J=2.1\text{Hz}$, $J=1.8\text{Hz}$), 7.50(dt, 2H,
 $J=8.6\text{Hz}$, $J=2.1\text{Hz}$), 7.40(dt, 1H, $J=7.9\text{Hz}$, $J=1.0\text{Hz}$), 7.26(ddd, 1H,
 $J=7.6\text{Hz}$, $J=5.1\text{Hz}$, $J=1.7\text{Hz}$), 3.04(s, 3H)

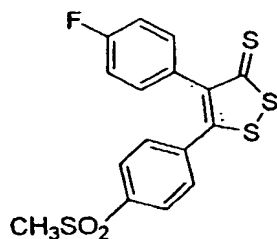
El Mass(M^+) : 365

Example 50

4-(4-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thion

e

Formula 54



195 mg (yield 63%) of the titled compound as a liquid was
 prepared in the same manner as in Example 39 except using 0.3 g of
 2-(4-fluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid
 ethyl ester instead of
 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid
 ethyl ester.

$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.90(d, 2H, $J=8.0\text{Hz}$), 7.44(d, 2H,
 $J=8.0\text{Hz}$), 7.09-7.04(m, 4H), 3.05(s, 3H)

El Mass(M^+) : 382

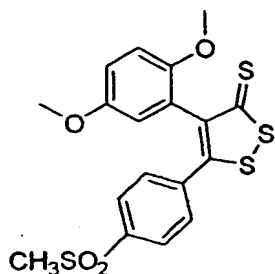
Melting point: 195-197°C

Example 51

4-(2,5-dimethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-

3-thione

Formula 55



180 mg (yield 60%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(2,5-dimethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

¹H-NMR(400MHz, CDCl₃) δ 7.87(d, 2H, J=8.4Hz), 7.51(d, 2H, J=8.4Hz), 6.87(dd, 1H, J=12.0Hz, J=2.8Hz), 6.78(d, 1H, J=12Hz), 6.62(d, 1H, J=2.8Hz), 3.72(s, 3H), 3.53(s, 3H), 3.03(s, 3H)

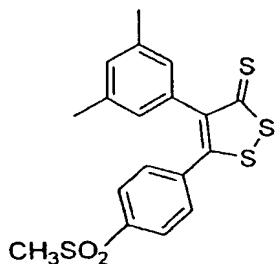
El Mass(M⁺) : 424

Melting point: 176-177 °C

Example 52

4-(3,5-dimethylphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione

Formula 56



210 mg (yield 66%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(3,5-dimethylphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid

ethyl ester instead of
2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid
ethyl ester.

¹H-NMR(400MHz, CDCl₃) δ 7.88(d, 2H, J=8.4Hz), 7.47(d, 2H, J=8.4Hz), 6.96(s, 1H), 6.69(s, 2H), 3.03(s, 3H), 2.37(s, 6H)

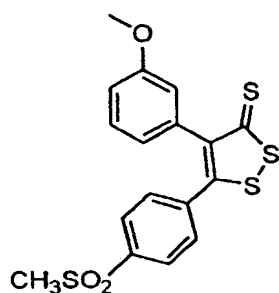
EI Mass(M⁺) : 392

Melting point: 164-165 °C

Example 53

5-(4-methanesulfonylphenyl)-4-(3-methoxyphenyl)-[1,2]dithiol-3-thione
one

Formula 57



210 mg (yield 66%) of the titled compound as a liquid was
prepared in the same manner as in Example 39 except using 0.3 g of
3-(4-methanesulfonylphenyl)-2-(3-methoxyphenyl)-3-oxo-propionic acid
ethyl ester instead of
2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid
ethyl ester.

¹H-NMR(400MHz, CDCl₃) δ 7.89(d, 2H, J=8.4Hz), 7.49(d, 2H, J=8.4Hz), 7.24(t, 1H, J=8.2Hz), 6.88(d, 1H, J=7.2Hz), 6.69(s, 1H), 6.65(d, 1H, J=7.2Hz), 3.71(s, 3H), 3.04(s, 3H)

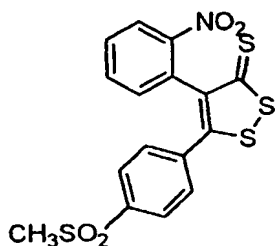
EI Mass(M⁺) : 394

Melting point: 212-213 °C

Example 54

5-(4-methanesulfonylphenyl)-4-(2-nitrophenyl)-[1,2]dithiol-3-thione

Formula 58



217 mg (yield 70%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-2-(2-nitrophenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.13(d, 1H, $J=6.8\text{Hz}$), 7.89(d, 2H, $J=8.4\text{Hz}$), 7.56-7.54(m, 4H), 7.01(d, 1H, $J=6.8\text{Hz}$), 3.04(s, 3H)

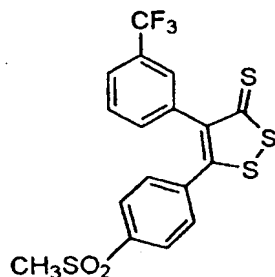
10 EI Mass(M^+) : 409

Melting point: 170-171 $^\circ\text{C}$

Example 55

5-(4-methanesulfonylphenyl)-4-(3-trifluoromethylphenyl)-[1,2]dithio I-3-thione

Formula 59



240 mg (yield 78%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-(3-trifluoromethylphenyl)-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.90(d, 2H, $J=8.4\text{Hz}$), 7.59(d, 1H, $J=7.6\text{Hz}$), 7.49(t, 1H, $J=8.0\text{Hz}$), 7.43(d, 2H, $J=8.4\text{Hz}$), 7.38(d, 1H, $J=7.6\text{Hz}$), 7.29(s, 1H), 3.04(s, 3H)

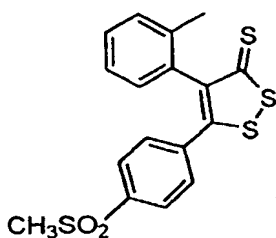
El Mass(M^+) : 432

5 Melting point: 188-189°C

Example 56

5-(4-methanesulfonylphenyl)-4-o-toryl- [1,2]dithiol-3-thione

Formula 60



10

173 mg (yield 56%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-o-toryl-propionic acid ethyl ester instead of

15 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.87(d, 2H, $J=8.4\text{Hz}$), 7.46(d, 2H, $J=8.4\text{Hz}$), 7.30(d, 1H, $J=7.6\text{Hz}$), 7.22-7.17(m, 2H), 6.96(d, 1H, $J=7.6\text{Hz}$), 3.04(s, 3H), 2.10(s, 3H)

20 El Mass(M^+) : 378

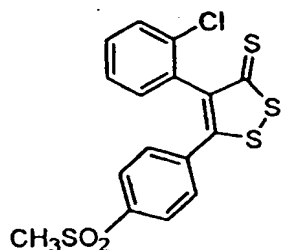
Melting point: 165-166°C

Example 57

4-(2-chlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thion

25 e

Formula 61



210 mg (yield 68%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(2-chlorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.90(d, 2H, $J=8.4\text{Hz}$), 7.53(d, 2H, $J=8.4\text{Hz}$), 7.43(dd, 1H, $J=9.2\text{Hz}$, $J=1.6\text{Hz}$), 7.32(m, 2H), 7.12(dd, 1H, $J=9.2\text{Hz}$, $J=1.6\text{Hz}$), 3.05(s, 3H)

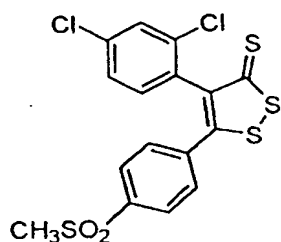
EI Mass(M^+) : 398

Melting point: 161-162°C

Example 58

4-(2,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione

Formula 62



198 mg (yield 64%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(2,4-dichlorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.94(d, 2H, $J=8.4\text{Hz}$), 7.50(d, 2H, $J=8.4\text{Hz}$), 7.43(s, 1H), 7.30(d, 1H, $J=8.4\text{Hz}$), 7.07(d, 1H, $J=8.4\text{Hz}$), 3.07(s, 3H)

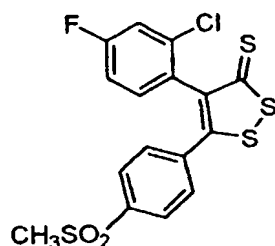
El Mass(M^+) : 433

5 Melting point: 176-177°C

Example 59

4-(2-chloro-4-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione

10 Formula 63



164 mg (yield 53%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(2-chloro-4-fluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.83(d, 2H, $J=8.4\text{Hz}$), 7.43(d, 2H, $J=8.4\text{Hz}$), 7.07(dd, 1H, $J=5.6\text{Hz}$, $J=2.4\text{Hz}$), 7.03(dd, 1H, $J=8.4\text{Hz}$, $J=6.0\text{Hz}$), 6.93(td, 1H, $J=6.0\text{Hz}$, $J=2.4\text{Hz}$), 2.97(s, 3H)

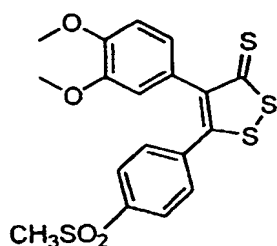
El Mass(M^+) : 416

Melting point: 184-185°C

Example 60

25 4-(3,4-dimethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione

Formula 64



155 mg (yield 50%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(3,4-dimethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.81(d, 2H, $J=8.4\text{Hz}$), 7.40(d, 2H, $J=8.4\text{Hz}$), 6.73(d, 1H, $J=8.4\text{Hz}$), 6.61(d, 1H, $J=2.0\text{Hz}$), 6.53(dd, 1H, $J=7.2\text{Hz}$, $J=2.0\text{Hz}$), 3.78(s, 3H), 3.66(s, 3H), 2.96(s, 3H)

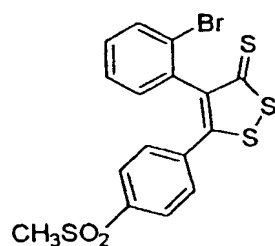
EI Mass(M^+) : 424

Melting point: 182-183°C

Example 61

15 4-(2-bromophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione

ne
Formula 65



186 mg (yield 60%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(2-bromophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.82(d, 2H, $J=8.4\text{Hz}$), 7.52-7.50(m, 1H), 7.46(d, 2H, $J=8.4\text{Hz}$), 7.25-7.23(m, 1H), 7.16-7.14(m, 1H), 7.01-7.00(m, 1H), 3.05(s, 3H)

El Mass(M^+) : 443

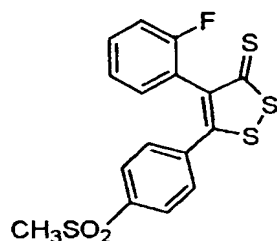
5 Melting point: 179-180 $^\circ\text{C}$

Example 62

4-(2-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione

e

10 Formula 66



170 mg (yield 55%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(2-fluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.82(d, 2H, $J=8.4\text{Hz}$), 7.42(d, 2H, $J=8.4\text{Hz}$), 7.30-7.29(m, 1H), 7.09-7.06(m, 2H), 6.94(t, 1H, $J=9.3\text{Hz}$), 3.05(s, 3H)

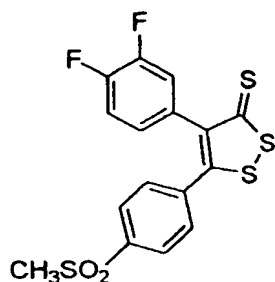
El Mass(M^+) : 382

Melting point: 173-174 $^\circ\text{C}$

Example 63

25 4-(2,4-difluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione

Formula 67



179 mg (yield 58%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(2,4-difluoro)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.85(d, 2H, $J=8.4\text{Hz}$), 7.42(d, 2H, $J=8.4\text{Hz}$), 7.12(dd, 1H, $J=16.8\text{Hz}$, $J=8.6\text{Hz}$), 6.87-6.84(m, 1H), 6.69-6.66(m, 1H), 3.0(s, 3H)

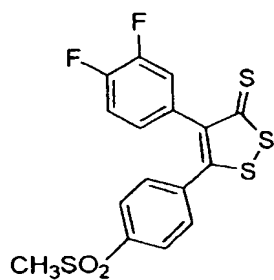
EI Mass(M^+) : 400

Melting point: 148-149 $^\circ\text{C}$

Example 64

4-(3,4-difluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione

Formula 68



182 mg (yield 59%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(3,4-difluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid

ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.86(d, 2H, $J=8.4\text{Hz}$), 7.38(d, 2H, $J=8.4\text{Hz}$), 7.05-7.01(m, 1H), 6.94-6.90(m, 1H), 6.74-6.72(m, 1H), 3.0(s, 3H)

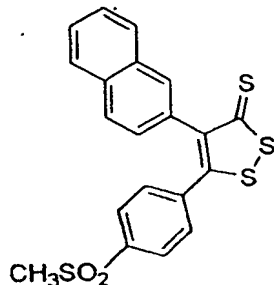
5 EI Mass(M^+) : 400
Melting point: 193-194 °C

Example 65

5-(4-methanesulfonylphenyl)-4-(naphthalene-2-yl)-[1,2]dithiol-3-thi

10 one

Formula 69



188 mg (yield 60%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-2-(naphthalene-2-yl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

20 $^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.93(d, 2H, $J=8.4\text{Hz}$), 7.70-7.65(m, 6H), 7.37-7.35(m, 3H), 3.04(s, 3H)

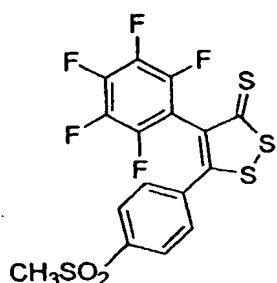
EI Mass(M^+) : 414

Example 66

5-(4-methanesulfonylphenyl)-4-pentafluorophenyl-[1,2]dithiol-3-thi

25 one

Formula 70



200 mg (yield 65%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-pentafluorophenyl-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 8.07(d, 2H, $J=8.4\text{Hz}$), 7.26(d, 2H, $J=8.4\text{Hz}$), 3.13(s, 3H)

EI Mass(M^+) : 454

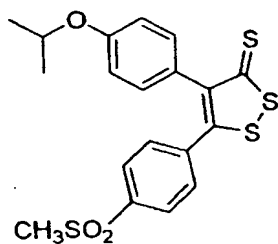
Melting point: 181-182 $^\circ\text{C}$

Example 67

4-(4-isopropoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3

-thione

Formula 71



210 mg (yield 68%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(4-isopropoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.90(d, 2H, $J=8.4\text{Hz}$), 7.47(d, 2H, $J=8.4\text{Hz}$), 7.06(d, 2H, $J=8.8\text{Hz}$), 6.84(d, 2H, $J=8.8\text{Hz}$), 4.52-4.50(m, 1H), 3.06(s, 3H), 1.32(s, 3H), 1.31(s, 3H)

El Mass(M^+) : 422

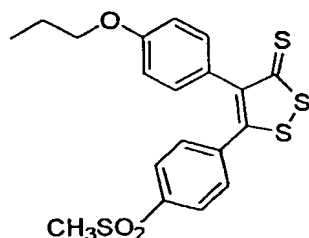
5 Melting point: 179-180 $^\circ\text{C}$

Example 68

5-(4-methanesulfonylphenyl)-4-(4-propoxyphenyl)-[1,2]dithiol-3-thi

one

10 Formula 72



207 mg (yield 67%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-(4-propoxyphenyl)-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.90(d, 2H, $J=8.4\text{Hz}$), 7.47(d, 2H, $J=8.4\text{Hz}$), 7.06(d, 2H, $J=8.8\text{Hz}$), 6.84(d, 2H, $J=8.8\text{Hz}$), 3.90(s, 3H), 3.05(s, 3H), 1.79-1.78(m, 2H), 1.19(t, 3H, $J=8.0\text{Hz}$)

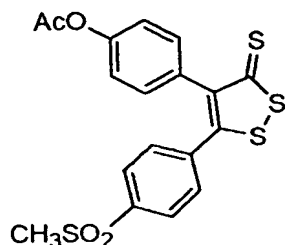
El Mass(M^+) : 422

Melting point: 177-178 $^\circ\text{C}$

Example 69

25 Acetic acid 4-[5-(4-methanesulfonylphenyl)-3-thioxo-3H-[1,2]dithiol-4-yl]phenyl ester

Formula 73



140 mg (yield 45%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(4-acetoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

¹H-NMR(400MHz, CDCl₃) δ 7.92(d, 2H, J=9.4Hz), 7.48(d, 2H, J=9.4Hz), 7.19(d, 2H, J=7.6Hz), 7.03(d, 2H, J=7.6Hz), 3.08(s, 3H), 2.49(s, 3H)

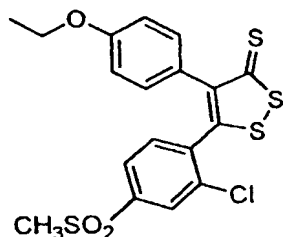
EI Mass(M⁺) : 422

Melting point: 241-243°C

Example 70

5-(2-chloro-4-methanesulfonylphenyl)-4-(4-ethoxyphenyl)-[1,2]dithiol-3-thione

Formula 74



170 mg (yield 55%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(2-chloro-4-methanesulfonylphenyl)-2-(4-ethoxyphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

¹H-NMR(400MHz, CDCl₃) δ 7.80(d, 1H, J=1.6Hz), 7.69(dd, 1H,

$J=6.4\text{Hz}$, $J=2.0\text{Hz}$), 7.32(d, 1H, $J=8.0\text{Hz}$), 6.88(d, 2H, $J=8.4\text{Hz}$), 6.62(d, 2H, $J=8.4\text{Hz}$), 3.81(q, 2H, $J=7.2\text{Hz}$), 2.98(s, 2H), 1.23(t, 3H, $J=4.0\text{Hz}$)

El Mass(M⁺) : 443

Melting point: 190-191 °C

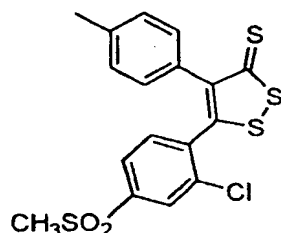
5

Example 71

5-(2-chloro-4-methanesulfonylphenyl)-4-p-toryl-[1,2]dithiol-3-thione

e

Formula 75



10

173 mg (yield 56%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(2-chloro-4-methanesulfonylphenyl)-3-oxo-2-p-toryl-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

15

¹H-NMR(400MHz, CDCl₃) δ 7.98(d, 1H, $J=1.6\text{Hz}$), 7.83(dd, 1H, $J=6.0\text{Hz}$, $J=2.0\text{Hz}$), 7.51(d, 1H, $J=8.0\text{Hz}$), 7.11(d, 2H, $J=8.4\text{Hz}$), 7.02(d, 2H, $J=8.4\text{Hz}$), 3.09(s, 3H), 2.32(s, 3H)

20

El Mass(M⁺) : 413

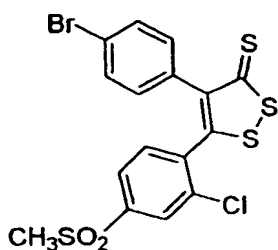
Melting point: 188-189 °C

Example 72

4-(4-bromophenyl)-5-(2-chloro-4-methanesulfonylphenyl)-[1,2]dithi

25 ol-3-thione

Formula 76



192 mg (yield 62%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(4-bromophenyl)-3-(2-chloro-4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.98(d, 1H, $J=1.6\text{Hz}$), 7.86(dd, 1H, $J=8.0\text{Hz}$, $J=1.6\text{Hz}$), 7.51(d, 1H, $J=8.0\text{Hz}$), 7.11(d, 2H, $J=8.4\text{Hz}$), 7.02(d, 2H, $J=8.4\text{Hz}$), 3.09(s, 3H)

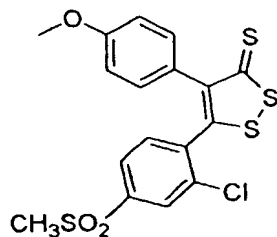
El Mass(M^+) : 477

Melting point: 194-195°C

Example 73

5-(2-chloro-4-methanesulfonylphenyl)-4-(4-methoxyphenyl)-[1,2]dithiol-3-thione

Formula 77



195 mg (yield 63%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(2-chloro-4-methanesulfonylphenyl)-2-(4-methoxyphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.99(d, 1H, $J=1.6\text{Hz}$), 7.87(dd, 1H, $J=8.0\text{Hz}$, $J=1.6\text{Hz}$), 7.52(d, 1H, $J=8.0\text{Hz}$), 7.12(d, 2H, $J=8.4\text{Hz}$), 7.03(d, 2H, $J=8.4\text{Hz}$), 4.25(s, 3H), 3.09(s, 3H)

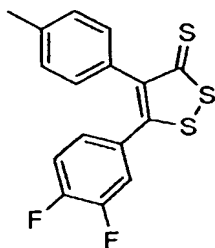
El Mass(M^+) : 428

5 Melting point: 192-193 $^\circ\text{C}$

Example 74

5-(3,4-difluorophenyl)-4-p-toryl-[1,2]dithiol-3-thione

Formula 78



10

293 mg (yield 52%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.5 g of 3-(3,4-difluorophenyl)-3-oxo-2-p-toryl-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

15

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.15(d, 2H, $J=7.6\text{Hz}$), 7.03-7.01(m, 3H), 6.98(d, 2H, $J=7.6\text{Hz}$), 2.33(s, 3H)

El Mass(M^+) : 336

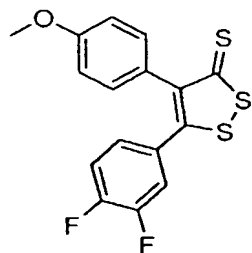
Melting point: 140-142 $^\circ\text{C}$

20

Example 75

5-(3,4-difluorophenyl)-4-(4-methoxyphenyl)-[1,2]dithiol-3-thione

Formula 79



25

274 mg (yield 52%) of the titled compound as a liquid was

prepared in the same manner as in Example 39 except using 0.5 g of
3-(3,4-difluorophenyl)-2-(4-methoxyphenyl)-3-oxo-propionic acid ethyl
ester instead of
2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid
ethyl ester.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.16(d, 2H, $J=7.6\text{Hz}$), 7.04-7.02(m,
3H), 6.99(d, 2H, $J=7.6\text{Hz}$), 3.82(s, 3H)

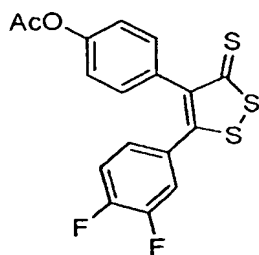
EI Mass(M^+) : 352

Melting point: 143-145 $^\circ\text{C}$

Example 76

Acetic acid 4-[5-(3,4-difluorophenyl)-3-thioxo-3H-[1,2]dithiol-4-yl]-
phenyl ester

Formula 80



267 mg (yield 51%) of the titled compound as a liquid was
prepared in the same manner as in Example 39 except using 0.5 g of
2-(4-acetoxyphenyl)-3-(3,4-difluorophenyl)-3-oxo-propionic acid ethyl
ester instead of
2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid
ethyl ester.

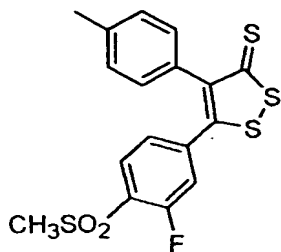
$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.17(d, 2H, $J=7.6\text{Hz}$), 7.05-7.03(m,
3H), 6.99(d, 2H, $J=7.6\text{Hz}$), 2.32(s, 3H)

EI Mass(M^+) : 380

Melting point: 147-149 $^\circ\text{C}$

Example 77

5-(3-fluoro-4-methanesulfonylphenyl)-4-p-toryl-[1,2]dithiol-3-thione
Formula 81



0.1 g of 5-(3,4-difluorophenyl)-4-p-toryl-[1,2]dithiol-3-thione which was prepared in the above example 74 was dissolved in dimethyl sulfoxide, and then 33 mg of sodium methanesulfinate was added thereto to let the mixture to react at 80°C for 3 hours. When the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The obtained organic layer was dried on anhydrous magnesium sulfate and then purified by flash chromatography to give 66 mg of the titled compound as a red solid (yield 56%).

¹H-NMR(400MHz, CDCl₃) δ 7.90-7.89(m, 1H), 7.15-7.12(m, 4H), 7.00-6.98(m, 2H), 3.21(s, 3H), 2.34(s, 3H)

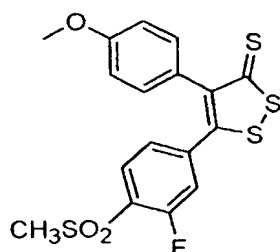
EI Mass(M⁺): 396

Melting point: 205-207 °C

Example 78

5-(3-fluoro-4-methanesulfonylphenyl)-4-(4-methoxyphenyl)-[1,2]dithiol-3-thione

Formula 82



58 mg (yield 50%) of the titled compound as a solid was prepared in the same manner as in Example 78 except using 5-(3,4-difluorophenyl)-4-(4-methoxyphenyl)-[1,2]dithiol-3-thione which was prepared in the above example 75 instead of 5-(3,4-difluorophenyl)-4-p-toryl-[1,2]dithiol-3-thione.

¹H-NMR(400MHz, CDCl₃) δ 7.85(t, 1H, J=1.2Hz), 7.17(dd, 1H,

$J=10.0\text{Hz}$, $J=2.0\text{Hz}$), 7.15(dd, 1H, $J=10.0\text{Hz}$, $J=2.0\text{Hz}$), 6.96(d, 2H, $J=8.8\text{Hz}$), 6.84(d, 2H, $J=8.8\text{Hz}$), 3.74(s, 3H), 3.20(s, 3H)

El Mass(M^+) : 352

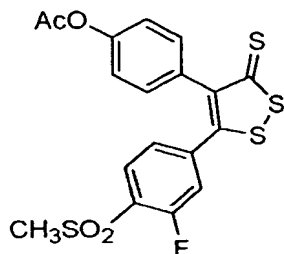
Melting point: 150-152 °C

5

Example 79

Acetic acid 4-[5-(3-fluoro-4-methanesulfonylphenyl)-3-thioxo-3H-[1,2]dithiol-4-yl]-phenyl ester

Formula 83



10

60 mg (yield 52%) of the titled compound as a solid was prepared in the same manner as in Example 78 except using acetic acid 4-[5-(3,4-difluorophenyl)-3-thioxo-3H-[1,2]dithiol-4-yl]-phenyl ester which was prepared in the above example 76 instead of 5-(3,4-difluorophenyl)-4-p-toryl-[1,2]dithiol-3-thione.

15

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.85(t, 1H, $J=1.2\text{Hz}$), 7.17-7.01(m, 4H), 6.92(d, 2H, $J=8.0\text{Hz}$), 3.14(s, 3H), 2.29(s, 3H)

El Mass(M^+) : 440

Melting point: 200-201 °C

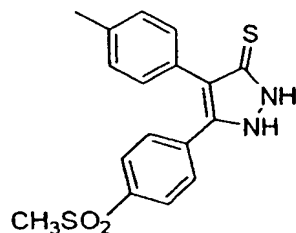
20

Example 80

5-(4-methanesulfonylphenyl)-4-p-toryl-[1,2]dihydropyrazole-3-thione

e

Formula 84



25

30 mg of potassium hydroxide was added to 0.1 g of 5-(4-methanesulfonylphenyl)-4-p-toryl-[1,2]dithiol-3-thione and then the mixture was dissolved in 5 ml of ethanol. Afterwards, 2 eq of hydrazine was added thereto to reflux at 80°C for 12 hours. The color change from red to yellow was observed. Ethanol was distilled from the reaction mixture under reduced pressure, and the resultant was diluted with water and extracted with ethyl acetate. The obtained organic layer was dried on anhydrous magnesium sulfate to distill the solvent. The resultant was recrystallized with n-hexane to give 56 mg of the titled compound as a yellow solid (yield 62%).

¹H-NMR(400MHz, CDCl₃) δ 7.86(d, 2H, J=7.6Hz), 7.58(d, 2H, J=7.6Hz), 7.22(d, 2H, J=8.0Hz), 7.16(s, 2H, J=8.0Hz), 3.04(s, 3H), 2.38(s, 3H)

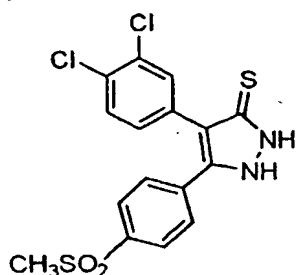
EI Mass(M⁺): 344

Melting point: 198-200°C

Example 81

4-(3,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-1,2-dihydropyrazole-3-thione

Formula 85



58 mg (yield 63%) of the titled compound as a liquid was prepared in the same manner as in Example 81 except using 0.1 g of 4-(3,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione instead of 5-(4-methanesulfonylphenyl)-4-p-toryl-[1,2]dithiol-3-thione.

¹H-NMR(400MHz, CDCl₃) δ 7.83(d, 2H, J=8.0Hz), 7.58(d, 2H, J=8.0Hz), 7.50(d, 1H, J=8.0Hz), 7.16(s, 1H), 7.07(d, 1H, J=8.0Hz), 3.20(s, 3H)

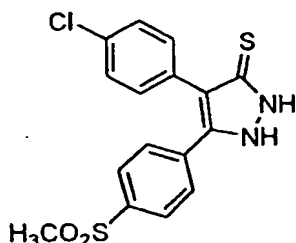
FAB Mass(M+1) : 399

Melting point: 192-193°C

Example 82

4-(4-chlorophenyl)-5-(4-methanesulfonylphenyl)-1,2-dihydropyrazole-3-thione

Formula 86



5

62 mg (yield 68%) of the titled compound as a liquid was prepared in the same manner as in Example 81 except using 0.1 g of 4-(4-chlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione instead of 5-(4-methanesulfonylphenyl)-4-p-toryl-[1,2]dithiol-3-thione.

10 $^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.80(d, 2H, $J=8.0\text{Hz}$), 7.54(d, 2H, $J=8.0\text{Hz}$), 7.42(d, 2H, $J=8.4\text{Hz}$), 7.28(d, 2H, $J=8.4\text{Hz}$), 3.19(s, 3H)

FAB Mass(M+1) : 365

Melting point: 211-213°C

15

Experiments1. Evaluation of selective COX-2 inhibitory activity1) Method

In order to pharmacologically determine the selective COX-2 inhibitory activity, the percentages of the COX-1 and COX-2 inhibition of the compounds of the present invention illustrated in the Examples were measured by the following methods.

20

a. Assay for the COX-1 inhibitory activity using U-937

U-937 human lymphoma cells (Korean Cell Line Bank, Seoul, Korea, Accession Number: 21593) were cultured and centrifuged. The collected cells were diluted with HBSS (x1, Hank's balanced salt solution) to a concentration of 1×10^6 cells/ml. 1 ml of the dilute cell solution was placed into each well of 12-well plates. 5 μl of 1 μM solution of a test compound in DMSO and 5 μl of DMSO as a control were added to the wells. The wells were incubated in CO_2 incubator at

25

30

37°C for 15 minutes. Separately, 10 mM stock solution of arachidonic acid in ethanol was diluted ten times in ethanol to prepare 1 mM solution of arachidonic acid. Arachidonic acid acts as a substrate. 10 μ l of the 1 mM solution of arachidonic acid was added to each well and incubated at CO₂ incubator at 37°C for 30 minutes. The cell solution of each well was placed in a centrifuge test tube and centrifuged at 10,000 rpm at 4°C for 5 minutes. The concentration of PGE2 in the collected cells and the supernatant was quantified by means of a monoclonal kit (Cayman Chemicals). The percentages of PGE2 inhibition in a group of the test compound-treated cells in relation to a group of the DMSO-treated cells were calculated. Based on the calculated values, the COX-1 inhibitory activities were evaluated.

b. Assay for the COX-2 inhibitory activity using RAW 264.7 cell line

2 x 10⁶ cells of RAW 264.7 cell line (Korean Cell Line Bank, Seoul, Korea, Accession Number: 40071) were inoculated into each well of 12-well plates. Each well was treated with 250 μ M of aspirin and incubated at 37°C for 2 hours. After the culture media were replaced with new culture media, the new culture media were treated with a test compound (30 nM) and incubated for 30 minutes. Then, each well was treated with interferon γ (100 units/ml) and lipopolysaccharide (LPS, 100 ng/ml) and incubated for 18 hours. The culture media were transferred to other test tubes. The concentration of PGE2 was quantified by means of the EIA kit (Cayman Chemicals).

2) Test results

The test results are presented in Table 1 below. The percentages of the COX inhibition were calculated according to the following equation:

$$\% \text{ Inhibition} = (\text{concentration of PGE2 in test compound-untreated sample} - \text{concentration of PGE2 in test compound-treated sample}) / (\text{concentration of PGE2 in test compound-untreated sample}) \times 100$$

35

Table 1
Cyclooxygenase (COX) Inhibition (%)

Samples	COX-1 (1 μ M)	COX-2 (30 nM)
Reference (Valdecoxib)	28.8	19
Example 39	15	36.6
Example 40	18.3	35.7
Example 41	20.1	24.5
Example 42	24.5	20.1
Example 43	19.3	38.4
Example 44	25.5	20.1
Example 45	19.6	22.1
Example 46	24.6	21.0
Example 47	22.5	21.4
Example 48	23.6	24.2
Example 49	28.0	19.5
Example 50	27.2	19.6
Example 51	27.6	19.8
Example 52	26.6	19.1
Example 53	26.7	21.6
Example 54	22.4	26.3
Example 55	27.6	20.2
Example 56	20.6	25.6
Example 57	20.7	21.1
Example 58	24.2	20.1
Example 59	23.2	19.7
Example 60	26.5	19.3
Example 61	23.3	20.1
Example 62	26.6	21.0
Example 63	20.3	21.3
Example 64	21.6	19.8
Example 65	22.6	20.1
Example 66	28.2	19.2
Example 67	27.5	23.3
Example 68	25.5	22.7
Example 69	24.8	21.3
Example 70	17.5	36.0
Example 71	20.3	21.0
Example 72	28.1	19.3
Example 73	25.6	20.1
Example 74	26.5	19.2
Example 75	26.6	19.6
Example 76	21.6	20.3
Example 77	15.2	31.5
Example 78	18.5	32.5
Example 79	19.5	30.2
Example 80	25.6	23.2

Example 81	24.9	24.6
Example 82	24.3	22.2

3) Evaluation

The *in vitro* test results about the percentages of the COX-1 and COX-2 inhibition are listed in Table 1.

As shown in Table 1, inhibition (%) ratios of COX-2 to COX-1 in
5 Examples 39 to 82 were significantly higher than that in the reference, Valdecoxib. This indicates that selective inhibition of COX-2 to COX-1 of the present compound is superior to that of the reference.

Industrial Applicability

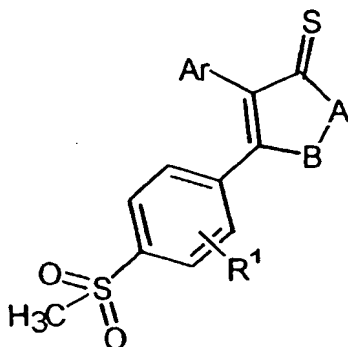
10 As apparent from the above description, the thione derivative according to the present invention is an alternative drug for conventional nonsteroidal antiinflammatory agents and is expected to be useful for treating patients with peptic ulcer disease, gastritis, regional enteritis, ulcerative colitis, diverticulitis, gastrorrhagia, osteoarthritis, or
15 rheumatoid arthritis.

While the present invention has been particularly shown and described with reference to exemplary embodiments thereof, it will be understood by those of ordinary skill in the art that various changes in form and details may be made therein without departing from the spirit
20 and scope of the present invention as defined by the following claims.

What is claimed is:

1. A thione derivative represented by formula 1:

Formula 1



5

wherein:

A and B each independently represent O, S, NR²; wherein R² represents hydrogen, C₁-C₄ alkyl, C₁-C₄ alkenyl, or aryl;

Ar represents aryl; heteroaryl; aryl or heteroaryl substituted with one to five radicals independently selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, trifluoromethyl, nitro, acetoxy, amino, C₁-C₃ alkylamino, C₁-C₃ dialkylamino, hydroxy, C₁-C₃ hydroxyalkyl, and thioxy; and

R¹ represents hydrogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, cyano, nitro, hydroxy, amino, C₁-C₄ alkylamino, or C₁-C₄ dialkylamino; or a non-toxic salt thereof.

2. The thione derivative according to claim 1 wherein

A and B each independently represent S or NH;

Ar represents phenyl; phenyl substituted with one to five radicals independently selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, trifluoromethyl, acetoxy, and nitro; pyridyl; or naphthyl;

R¹ represents hydrogen or halogen;

or a non-toxic salt thereof.

25

3. The thione derivative according to claim 1 or claim 2, which is selected from the group consisting of:

4-(4-ethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thio

ne;
4-(4-bromophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thio
ne;
5-(4-methanesulfonylphenyl)-4-toryl-[1,2]dithiol-3-thione;
5-(4-methanesulfonylphenyl)-4-phenyl-[1,2]dithiol-3-thione;
5-(4-methanesulfonylphenyl)-4-methoxyphenyl-[1,2]dithiol-3-thion
e;
5-(4-methanesulfonylphenyl)-4-(2-trifluoromethylphenyl)-[1,2]dithio
l-3-thione;
4-(4-chlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thion
e;
4-(3,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-t
hione;
5-(4-methanesulfonylphenyl)-4-pyridine-4-yl-[1,2]dithiol-3-thione;
5-(4-methanesulfonylphenyl)-4-pyridine-3-yl-[1,2]dithiol-3-thione;
5-(4-methanesulfonylphenyl)-4-pyridine-2-yl-[1,2]dithiol-3-thione;
4-(4-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thion
e;
4-(2,5-dimethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-
3-thione;
4-(3,5-dimethylphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-t
hione;
5-(4-methanesulfonylphenyl)-4-(3-methoxyphenyl)-[1,2]dithiol-3-thi
one;
5-(4-methanesulfonylphenyl)-4-(2-nitrophenyl)-[1,2]dithiol-3-thione
;
5-(4-methanesulfonylphenyl)-4-(3-trifluoromethylphenyl)-[1,2]dithio
l-3-thione;
5-(4-methanesulfonylphenyl)-4-o-toryl-[1,2]dithiol-3-thione;
4-(2-chlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thion
e;
4-(2,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-t
hione;
4-(2-chloro-4-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithi
ol-3-thione;
4-(3,4-dimethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-
3-thione;

4-(2-bromophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thio
 ne;
 4-(2-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thion
 e;
 5 4-(2,4-difluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-t
 hione;
 4-(3,4-difluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-t
 hione;
 5-(4-methanesulfonylphenyl)-4-naphthalene-2-yl-[1,2]dithiol-3-thio
 10 ne;
 5-(4-methanesulfonylphenyl)-4-pentafluorophenyl-[1,2]dithiol-3-thi
 one;
 4-(4-isopropoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3
 -thione;
 15 5-(4-methanesulfonylphenyl)-4-(4-propoxyphenyl)-[1,2]dithiol-3-thi
 one;
 acetic acid 4-[5-(4-methanesulfonylphenyl)-3-thioxo-3H-[1,2]dithiol
 -4-yl]phenyl ester;
 5-(2-chloro-4-methanesulfonylphenyl)-4-(4-ethoxyphenyl)-[1,2]dithi
 20 ol-3-thione;
 5-(2-chloro-4-methanesulfonylphenyl)-4-*p*-toryl-[1,2]dithiol-3-thion
 e;
 4-(4-bromophenyl)-5-(2-chloro-4-methanesulfonylphenyl)-[1,2]dithi
 ol-3-thione;
 25 5-(2-chloro-4-methanesulfonylphenyl)-4-(4-methoxyphenyl)-[1,2]di
 thiol-3-thione;
 5-(3-fluoro-4-methanesulfonylphenyl)-4-*p*-toryl-[1,2]dithiol-3-thione
 ;
 5-(3-fluoro-4-methanesulfonylphenyl)-4-(4-methoxyphenyl)-[1,2]dit
 30 hiol-3-thione;
 acetic acid 4-[5-(3-fluoro-4-methanesulfonylphenyl)-3-thioxo-3H-
 [1,2]dithiol-4-yl]-phenyl ester;
 5-(4-methanesulfonylphenyl)-4-*p*-toryl-1,2-dihydropyrazole-3-thion
 e;
 35 4-(3,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-1,2-dihydropyr
 azole-3-thione; and
 4-(4-chlorophenyl)-5-(4-methanesulfonylphenyl)-1,2-dihydropyrazo

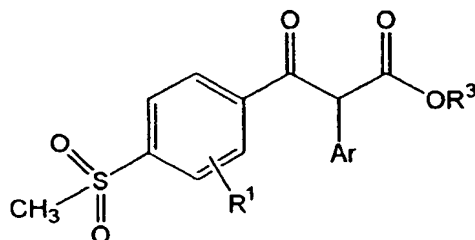
le-3-thione

or a non-toxic salt thereof.

4. A propionic acid derivative represented by formula 2:

5

Formula 2



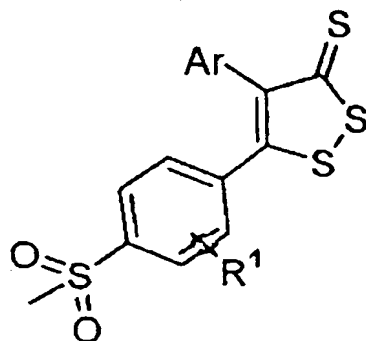
wherein, R^1 and Ar are as defined in claim 1 and R^3 represents C_1 - C_4 alkyl.

10

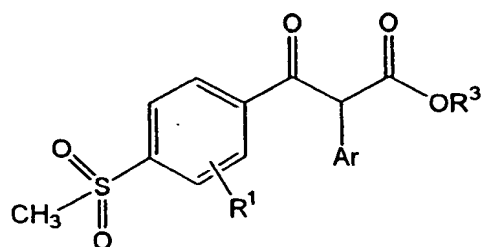
5. A method for preparing a thione derivative of formula 1a or a non-toxic salt thereof, comprising reacting a propionic acid derivative of formula 2 with phosphorus pentasulfide, Lawesson's Reagent, beta-oxothiostic acid, or potassium beta-oxothiostate:

15

Formula 1a



Formula 2



wherein:

R^1 and Ar are as defined in claim 1;

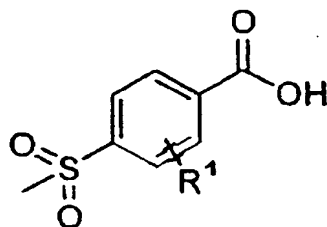
R^3 represents C_1 - C_3 alkyl.

5

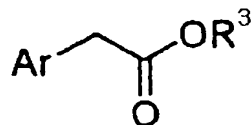
6. A method according to claim 5, wherein the propionic acid derivative of formula 2 is prepared by reacting a methanesulfonylbenzoic acid derivative of formula 3 with a aryl acetate derivative of formula 4 in the presence of a base;

10

Formula 3



Formula 4



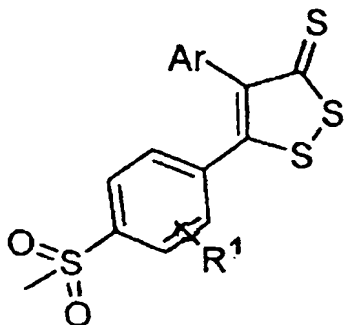
wherein:

R^1 and Ar are as defined in claim 1 and R^3 represents C_1 - C_4 alkyl.

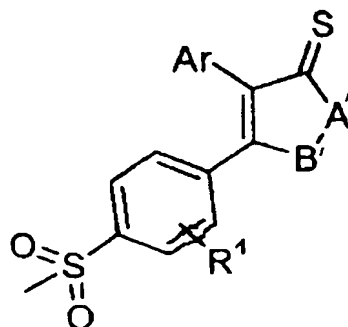
15

7. A method for preparing a thione derivative of formula 1b or a non-toxic salt thereof, comprising reacting a thione derivative of formula 1a with $\text{NHR}^2\text{NH R}^2$ or $\text{NH R}^2\text{OH}$ in the presence of a base;

5 Formula 1a



Formula 1b



wherein:

- 10 A' and B' each independently represent S or NR^2 , provided that A' and B' are not simultaneously S; and
Ar and R^2 are as defined in claim 1.

8. A pharmaceutical composition comprising a therapeutically
15 effective amount of a thione derivative or a non-toxic salt thereof according to claim 1 to claim 3 as an active ingredient and a pharmaceutically acceptable carrier for the treatment of fever, pain, and inflammation.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR2003/002553

A. CLASSIFICATION OF SUBJECT MATTER**IPC7 C07D 339/04**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean patents and applications for inventions since 1975: IPC as aboveElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS, Delphion, Medline**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PARK J et al., "Screening of the anticancer potential of celecoxib and its derivatives" In Yakche Hakhoechi, 2003 JUNE, Vol. 33(2), pp 105-112 & CA 140:246247 see the whole document	1-3, 5-8
P, X	KR 2004-42246 A (CJ CORPORATION) 20 MAY 2004 see the whole document	1-8
A	US 5470871 A (LABORATOIRES DE THERAPEUTIQUE MODERNE) 28 NOVEMBER 1995 see the whole document	1-8
A	US 4760078 A (MITSUI TOATSU CHEMICALS INC.) 27 JULY 1988 see the whole document	1-8
A	SCHRIER DJ et al., "The pharmacologic effects of 5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-thiadiazole-2(3H)-thione, choline salt (CI-986), a novel inhibitor of arachidonic acid metabolism in models of inflammation, analgesia and gastric irritation" In Prostaglandins, 1994, JANUARY, Vol. 47(1), pp 17-30 see the whole document	1-8

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family


Date of the actual completion of the international search

28 JULY 2004 (28.07.2004)

Date of mailing of the international search report

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